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(54) **DERIVATIVES OF ACYL-PIPERAZINIL-PYRIMIDINS, PREPARATION THEREOF AND APPLICATION AS MEDICAMENTS**

DERIVATE VON ACYL-PIPERAZINIL-PYRIMIDINEN, IHRE HERSTELLUNG UND VERWENDUNG ALS MEDIKAMENT

DERIVES D'ACYLE-PIPERAZINIL-PYRIMIDINES, PREPARATION ET UTILISATION DE CES DERIVES COMME MEDICAMENTS

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(56) References cited:
EP-A- 0 115 713
EP-A- 0 382 637
EP-A- 0 497 659
WO-A-94/14779
US-A- 4 547 505

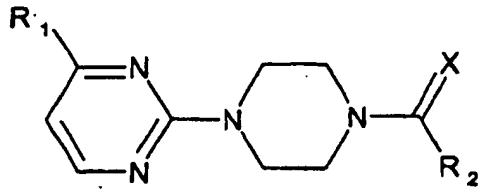
Remarks:
The file contains technical information submitted after the application was filed and not included in this specification

EP 1 006 110 B1

Description

FIELD OF THE INVENTION

[0001] The present invention relates to new acyl-piperazinyl-pyrimidines of the general formula (I), to their physiologically acceptable salts, to procedures for their preparation, to their use in the preparation of medicaments for the therapy of humans and/or as veterinary medicaments and to the pharmaceutical compositions which contain said compounds.

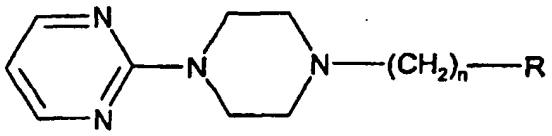


(I)

[0002] The new compounds object of the present invention can be used in the pharmaceutical industry as intermediates and for the preparation of medicaments.

BACKGROUND OF THE INVENTION

[0003] In our patents EP 382 637 and EP 497 659 we have described different derivatives of alkyl-piperazinyl-pyrimidines of the general formula (II) with ansiolytic and or tranquillising properties.



(II)

[0004] European patent EP-0 115 713 refers to (piperazinyl-1)2-pirimidines, with substituents in position 4 of piperazine, consisting of an alkylcarbonyl group, alkylcarbonyl substituted by an amino or substituted amino group, an alkylcarboxylic or alkylcarboxylate group, or a substituted cabonylalkyl group, having psycotropic activity by means of a dopaminergic mechanism.;

[0005] PCT application WO 94/14779, refers to (piperazinyl-1)-4-pirimidines, with substituents in position 4 of piperazine, only consisting of linear or branched alkyl chains of up to 4 atoms, optionally terminating with a phenyl group which may be substituted, having antagonist activity of the 5-HT1 receptor and which may be used in the treatment of prevention of upsets related to excessive vasodilatation;

[0006] US-4.547.505 patent refers to new pharmacologically active compounds, whose general formulation includes a piperazine, where one of the nitrogen atoms is substituted by groups, namely pyrimidine or others, and the other nitrogen atom is replaced by a subtituted acyl group, and which possesses analgesic activity.

[0007] We have now discovered that the addition of a substituent to position 4 of the pyrimide and the substitution of an alkyl radical with an acyl radical gives rise to the new compounds of general formula (I). Said compounds show useful biological properties which makes them especially useful for their use in therapy in humans and veterinary therapy. The compounds of the present invention are useful as agents which act on the central nervous system in mammals including humans. In particular, the new compounds are useful as sedatives, anti-convulsants, sleep-inducing agents and general anaesthetics.

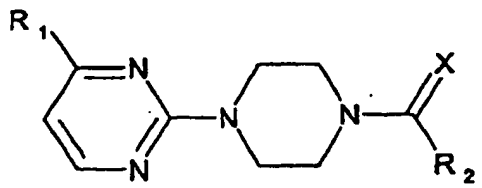
BRIEF DESCRIPTION OF THE FIGURES

[0008] Figure 1 shows the results of the sedative activity of some of the compounds of the invention, as determined by reduction in locomotive activity.

DETAILED DESCRIPTION OF THE INVENTION

[0009] The present invention provides new compounds capable of inducing conscious sedation, of acting as sleep-inducing agents, anti-convulsants, analgesics, muscular relaxants, anti-tusigenics, ansiolytics, anti-psychotics, anti-depressants, anti-cerebral ischeamics, anti-migraine agents, agents useful for sleep disorders, agents for neurodegenerative diseases, agents for cognitive disorders and Alzheimer's disease, and agents capable of inducing or maintaining general anaesthesia, when administered by an appropriate method at a suitable dosage level.

[0010] The compounds of the present invention are represented by the general formula (I)



(I)

where

X is an oxygen or sulphur atom;

R_1 is a C_{1-4} alkoxy or trifluoromethyl radical;

R_2 is a C_{1-6} alkyl radical; C_{3-6} saturated cycloalkyl; heterocycloalkyl consisting of a ring of 3 to 6 atoms in which the heteroatom is selected from an atom of oxygen, sulphur or nitrogen, optionally N-substituted; phenyl optionally substituted with 1, 2 or 3 identical or different substituents selected from fluorine, chlorine, bromine, amino, acetamido, nitro, methyl, trifluoromethyl and methoxy; arylalkyl consisting of a C_{1-3} alkyl group substituted by a phenyl radical optionally substituted by 1, 2 or 3 identical or different substituents selected from fluorine, chlorine, bromo, amino, acetamido, nitro, methyl, trifluoromethyl and methoxy; heteroaryl consisting of a 5 or 6 heteroatom ring, optionally substituted, or of fused heteroaromatic systems optionally substituted, of 9 or 10 atoms consisting of 1 or 2 heteroatoms selected from oxygen, sulphur and nitrogen, selecting the aforementioned substituents from flourine, chlorine, bromine, amino, acetamido, nitro, methyl, trifluoromethyl and methoxy; and heteroarylalkyl consisting of an alkyl group of 1 to 3 carbon atmos substituted with a heteroaryl radical consisting of a 5 or 6 member heteroaromatic ring, optionally substituted, or of fused 9 to 10 member heteroaromatic systems, optionally substituted with 1 or 2 heteroaryl radical consisting of a 5 or 6 member heteroaromatic ring, optionally substituted, or of fused 9 to 10 member heteroaromatic systems, optionally substituted with 1 or 2 heteroatoms selected from oxygen, sulphur and nitrogen, selected the aforementioned substituents from fluorine, chlorine, bromine, amino, acetamido, nitro, methyl, trifluoromethyl and methoxy; and their physiologically acceptable salts.

[0011] In the present invention, the term C_{1-4} "alkoxy" represents a radical OR_3 in which R_3 is a saturated linear or branched carbon chain containing 1 to 4 atoms, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, *sec*-butoxy o *tert*-butoxy for example.

[0012] The term "alkyl" represents a radical derived from a saturated linear or branched hydrocarbon. The term C_{1-6} alkyl represents a linear or branched chain alkyl radical containing 1 to 6 atoms of carbon, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, isopentyl, neopentyl and hexyl for example.

[0013] The term C_{3-6} saturated "cycloalkyl" represents a saturated ring of 3 to 6 atoms of carbon, such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl for example.

[0014] The term "heterocycloalkyl" represents a ring of 3 to 6 atoms of which there is a heteroatom such as an oxygen atom or an atom of sulphur, such as a 2-aziridinyl, 2-tetrahydrofuryl, 3-tetrahydrofuryl, 2-tetrahydrothienyl, 3-tetrahydrothienyl for example, or an atom of nitrogen which may or may not be substituted, such as 2-azetidinyl, 2-piperidinyl, 3-piperidinyl or 4-piperidinyl for example.

[0015] The term "aryl" represents an unsubstituted or substituted phenyl radical. with 1, 2 or 3 identical or different substituents such as fluorine, chlorine, bromine, amino, acetamido, nitro, methyl, triflouromethyl or methoxy, such as 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-bromophenyl, 3-bromorophenyl, 4-bromophenyl, 2-aminophenyl, 3-aminophenyl, 4-aminophenyl, 2-nitrophenyl, 3-nitrophenyl, 4-nitophenyl, 2-acetamidophenyl, 3-acetamidophenyl, 4-acetamidophenyl, 2-nitrophenyl, 3-nitrophenyl, 4-nitrophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-(trifluoromethyl)phenyl, 3-(trifluoromethyl)phenyl, 4-(trifluoromethyl)phenyl, 2-metoxyphenyl, 3-metoxyphenyl, 4-metoxyphenyl, 2,3-difluorophenyl, 3,4-difluorophenyl, 2,4-difluorophenyl, 2,3-dibromophenyl, 3,4-dibromophenyl, 2,4-dibromophenyl, 2,3-dimethylphenyl, 3,4-dimethylphenyl, 2,4-dimethylphe-

nyl, 2,3-dimethoxyphenyl, 3,4-dimethoxyphenyl, 2,4-dimethoxyphenyl for example.

[0016] The term "arylalkyl" represents a linear or branched chain of 1 to 3 atoms of carbon which is substituted with an aryl radical, according to the hereinbefore definition of "aryl", and which includes substituents such as phenylmethyl, 1-phenylethyl, 2-phenylethyl, 3-phenylethyl, 3-phenylpropyl, as well as other radicals in which the aromatic ring is substituted with groups such as fluorine, chlorine, bromine, amino, acetamido, nitro, methyl, trifluoromethyl or methoxy.

[0017] The term "heteroaryl" represents a substituted or unsubstituted heteraromatic ring of 5 or 6 members or unsubstituted or substituted fused heteroaromatic systems of 9 or 10 members consisting of 1 or 2 heteroatoms such as nitrogen, oxygen or sulphur, with the substituent groups being groups such as fluorine, chlorine, bromine, amino, acetamido, nitro, methyl, trifluoromethyl or methoxy, such as 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 3-methyl-2-thienyl, 5-methyl-2-thienyl, 3-methoxy-2-thienyl, 3-chloro-2-thienyl, 5-chloro-2-thienyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-indolyl, 3-indolyl, 2-benzo[b]thienyl, 3-benzyo[b]thienyl, 3-chloro-2-benzo[b]thienyl, pirazolyl, imidazolyl, pyrimidinyl, piridazinyl, pirazinyl, benzimidazolyl, quinolyl, oxazolyl and thiazolyl for example.

[0018] The term "heteroarylalkyl" represents an alkyl group of 1 to 3 atoms of carbon which is substituted with a heteroaryl radical, according to the hereinbefore definition of "heteroaryl", and which includes substituents such as 2-thienylmethyl, 2-benzo[b]thienylmethyl and 3-(4-chloropyrazolyl)propyl.

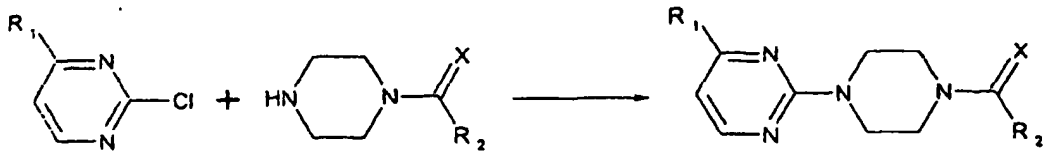
[0019] The new compounds of general formula (I) may contain an asymmetric carbon atom and can therefore be prepared as optical isomers or racemates. The racemates of compounds (I) can be resolved into their optical isomers using conventional methods, such as separation by chiral chromatography or fractionated crystallisation from their diasteroisomer salts for example. Similarly, they can also be obtained from asymmetric synthesis using chiral precursors.

[0020] The present invention also relates to physiologicaly acceptable salts of the compounds of general formula (I), in particular addition salts of mineral acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid and addition salts of organic acids such as *p*-toluensulphonic acid or methansulphonic acid.

[0021] The new derivatives of general formula (I), in which X is an atom of oxygen and R_1 and R_2 have the hereinbefore defined meaning, can be prepared according to methods A or B which are described below.

METHOD A:

[0022] The compounds of general formula (I) can be prepared by reacting the derivative of chloropyrimidine (III), where R_1 has the hereinbefore defined meaning, with a derivative of piperazine of general formula (IV) in which X and R_2 have the hereinbefore defined meaning.

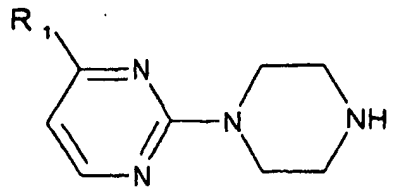


(III) (IV) (I)

[0023] The reaction is carried out in an organic solvent, for example in an chlorinated hydrocarbon such as dichloromethane or chloroform, a linear or cyclic ether such as 1,2-dimethoxyethane, tetrahydrofurane or dioxane, a aprotic polar solvent such as pyridine, dimethylsulphoxide or dimethylformamide or any other type of solvent appropriate for carry out a aromatic nucleophilic substitution reaction. The reaction can be carried out in the presence of a mineral or organic base such as an aliphatic amine, preferably triethylamine or M-methylmorphine by stirring at a temperature lying between room temperature and the boiling point of the solvent for a period of time lying between ten minutes and twenty-four hours, the preferring conditions being a period of time between thirty minutes and five hours.

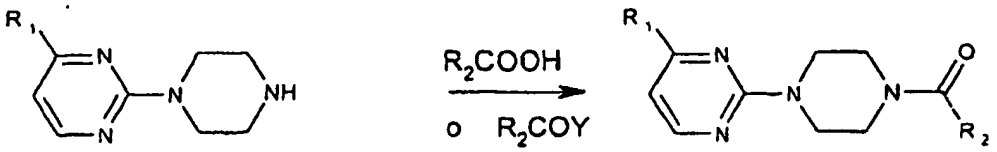
METHOD B:

[0024] By reaction of the amine of formula (V):



(V)

in which R_1 has the hereinbefore defined meaning with a carboxylic acid of the general formula R_2COOH (VI), in which R_2 has the hereinbefore defined meaning, or with a salt of said acid or also with a derivative reagent R_2COY (VII).



(V) (I)

[0025] Examples of salts include salts of alkali metals such as sodium salts and potassium salts, alkaline earth salts such as calcium salts and magnesium salts, ammonium salts, and salts of organic bases such as triethylamine, trimethylamine, pyridine and picoline.

[0026] Examples of derivative reagents of general formula R_2COY (VII) in which Y is a halogen atom preferably a chlorine atom or a bromine atom, an azide group ($-N_3$), a 1-imidazolyl, a $O-CO-R_4$, in which R_4 can be an alkyl or aryl radical of 1 to 6 carbon atoms, preferably substituted with one or several halogen atoms, or a group OR_5 where R_5 represents an aromatic group of one or two rings substituted with one or several halogen atoms or nitro radicals, the preferred groups being 4-nitrophenyl, 2,4-dinitrophenyl, pentachlorophenyl, pentafluorophenyl, 1-benzotriazolyl o N-succinimide. Similarly, instead of using the aforementioned derivative reagents. compounds of general formula (I) can be prepared directly by reaction of the amine (V) with the carboxylic acid or general formula (VI). In this case it is preferable that the reaction proceeds in the presence of reagents that activate the carbonyl groups such as N.N'-dicyclohexylcarbodiimide, diisopropylcarbondiimide or 3-(3-dimethylamino)propyl-1-ethycarbodiimide. This reaction can also be carried out using the said carbodiimidas in the presence of 1-benzotriazol or N-hydroxysuccinimide. The acids of general formula (VI) and the amine of formula (V) also react directly in the presence of N,N'-carbonyldiimidazol or of propanophosphonic acid anhydride.

[0027] The reaction is carried out in an organic solvent, for example in an chlorinated hydrocarbon such as dichloromethane or chloroform, a linear or cyclic ether such as 1,2-dimethoxyethane, tetrahydrofurane or dioxane, a aprotic polar solvent such as pyridine, dimethylsulphoxide or dimethylformamide or any other type of solvent appropriate for carry out a aromatic nucleophilic substitution reaction. The reaction can be carried out in the presence of a mineral or organic base such as an aliphatic amine, preferably triethylamine or M-methylmorphine by stirring at a temperature lying between room temperature and the boiling point of the solvent for a period of time lying between ten minutes and twenty-four hours, the preferring conditions being a period of time between thirty minutes and five hours.

METHOD C

[0028] The new derivatives of general formula (I), in which X is an atom of sulphur and R_1 and R_2 have the hereinbefore defined meaning, can be prepared according to the following method.

[0029] By treating a compound of a compound of general formula (I), in which R_1 and R_2 have the hereinbefore defined meaning and in which X is an atom of oxygen, with Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphaethano-2,4-disulphuro) or with phosphorous pentasulphide, the corresponding thioamides are obtained in which X is a sulphur atom:

[0030] The reaction is carried out in an organic solvent such as toluene, benzene, heptane, pyridine or tetrahydrofurane. The reaction is continually shaken at a temperature lying between room temperature and the boiling point of the solvent for a period of time of between one hour and twenty-four hours, preferably carrying out the reaction at 80°C for a time between one hour and sixteen hours.

METHOD D:

[0031] The salts of the compounds of general formula (I) can be prepared by reaction with a mineral acid such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid or with an organic acid such as *p*-toluensulphonic acid or methansulphonic acid in an appropriate solvent such as methanol, ethanol, ethyl ether, ethyl acetate, acetonitrile or acetone, being obtained with the normal precipitation techniques or crystallisation of the corresponding salts.

[0032] The invention provides pharmaceutical compositions which comprise, as well as a pharmaceutically acceptable excipient, at least one compound of general formula (I) or one of their physiologically acceptable salts. The invention also relates to the use of a compound of general formula (I) and their physiologically acceptable salts in the elaboration of a medicament with activity in the mammalian, central nervous system, including activity in the human central nervous system in particular, in the manufacture of a medicament with sedative, anticonvulsive, sleep-inducing and general anaesthetic activity.

[0033] In the examples which follow the preparation of new compounds according to the invention is indicated. Also described are some typical forms of use for the different fields of application, as well as medicinal formulas applicable to the compounds of the invention.

METHOD A:

Example 1. Preparation of 2-[4-(2-furylcarbonyl)-1-piperazinyl]-4-methoxy-pyrimidine.

[0034] A solution of 1.0 g (6.92 mmol) of 2-chloro-4-methoxypyrimidine, 1.49 g (8,30 mmol) of 1-(2-furylcarbonyl) piperazine and 1.39 g (13.84 mmol) of triethylamine in 20 mL of n-butanol is maintained under gentle reflux conditions overnight. The solvent is evaporated off under reduced pressure and the crude residue is diluted in chloroform and washed in water. The organic phase is dried over $NaSO_4$ and evaporated to dryness to give a crude product which is purified using silica-gel chromatography eluting with ethyl acetate/petroleum ether 70:30 to yield an oil which solidifies when left to stand. The solid is suspended in petroleum ether to yield 1.4 g (4.86 mmol) of 2-[4-(2-furylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine. m.p. = 85-86°C.

METHOD B:

Example 3. Preparation of 4-methoxy-2-4-(2-thienylcarbonyl)-1-piperazinyl] pyrimidine

[0035] A solution of 1.0 g (5.15 mmol) of 4-methoxy-2-(1-piperazinyl)pyrimidine and 1 mL (7.18 mmol) of triethylamine in 30 mL of CH_2Cl_2 is cooled to 0° C and 0.76 g (5.18 mmol) of 2-thienylcarbonyl chloride slowly added. The solution is kept at 0° C for an hour and then the temperature allowed to rise to room temperature. The organic phase is washed with H_2O, dried over $NaSO_4$ and the solvent removed under reduced pressure. The crude residue is dissolved in ethyl ether crystallising 1.0 g (3.28 mmol) of 4-methoxy-2-[4-(2-thiencarbonyl)-1-piperazinyl]pryimidine. m.p. = 71-73° C

Example 12. Preparation of 4-methoxy-2-[4-(3-thienylcarbonyl)-1-piperazinyl] pyrimidine.

[0036] To a solution of 1.0 g (7.81 mmol) of 3-thienylcarboxylic acid and 1 mL (7.86 mmol) of triethylamine in 30 mL of CH_2Cl_2 cooled to 0° C 0.84 g (7.81 mmol) of ethyl chloroformiate are added. The mixture is maintained at 0° C for 20 minutes and then 1.5 g (7.81 mmol) of 4-methoxy-2-(1-piperazinyl) pyrimidine dissolved in 10 mL of CH_2Cl_2 are

added to the solution. The temperature is allowed to rise to room temperature and the solution continually stirred for 2 hours and the organic phase is washed with H_2O, dried over $NaSO_4$ and the solvent evaporated off under reduced pressure. The resulting oil is treated with ethyl ether to yield a solid which is recrystallised from ethanol/H_2O to give 0.8 g (2.63 mmol) of 4-methoxy-2-[4-(3-thienylcarbonyl)-1-piperazinyl]pyrimidine. m.p. = 90-92° C.

Example 20. Preparation of 2-[4-(2-inolylcarbonyl)-1-piperazinyl]-4-methoxy pyrimidine.

[0037] To a solution of 0.83 g (5.15 mmol) of indol-2-carboxylic acid in 15 mL of dry THF 0.83 g (5.15 mmol) of N, N'-carbonyldiimidazol is added. After 30 minutes 1.0 g (5.15 mmol) of 4 methoxy-2-(1-piperazinyl) pyrimidine is added to the solution and it is left overnight with continuous stirring. The solvent is eliminated under reduced pressure and H_2O added. This produces a precipitate which is filtered and dried, to give 1.7 g (5.04 mmol) of 2-[4-(2-indolylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine. m.p. = 202-203° C.

METHOD C

Example 54. Preparation of 4-methoxy-2-(4-thiobenzoyl-1-piperazinyl)pyrimidine.

[0038] 0.56 g (1.9 mmol) of 2-(4-benzoyl-1-piperazinyl)-4-methoxypyrimidine are dissolved in 25 mL of dry toluene, and 0.46 g (1.14 mmol) of Lawesson's reagenr (2,4-bis(4-methoxyphenyl)-1,32,4-dithiadiphosphaethano-2,4-disulphide) added. The mixture is heated to 80-90° C for 16 hours. Ethyl ether is added, basic water is used to wash the residue and the organic extract is dried with $NaSO_4$ and the solvent evaporated off under reduced pressure. The resulting crude residue is crystallised with ethyl ether-petroleum ether to give 160 mg (0.5 mmol) of 2-(4-thiobenzoyl-1-piperazinyl)-4-methoxypyrimidine. m.p. = 125-129° C.

METHOD D:

Example 2. Preparation of 2-[4-(2-furylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine chlorohydrate.

[0039] 1.0 g (3.47 mmol) of 2-[4-(2-furylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine in ethyl acetate and a few drops of a solution of ethyl ether/hydrochloric acid are added, thus obtaining a precipitate which is filtered and dried, to yield 1.07 g (3.29 mmol) of 2-[4-(2-furylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine chlorohydrate. m.p. = 162-164° C.

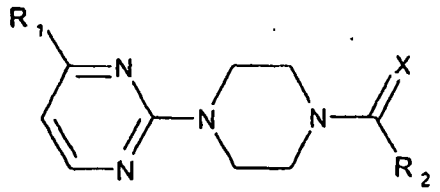
Example 4. Preparation of 4-methoxy-2-[4-(2-thienylcarbonyl)-1-piperazinyl] pyrimidine chlorohydrate.

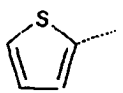
[0040] 1.0 g (3.29 mmol) of 4-methoxy-2-[4-(2-thienylcarbonyl)-1-piperazinyl] pyrimidine is dissolved in acetone and a few drops of a solution of ethyl ether/hydrochloric acid are added, thus obtaining a precipitate which is filtered and dried, to yield 1.05 g (3.08 mmol) of 4-methoxy-2-[4-(2-thienylcarbonyl)-1-piperazinyl] pyrimidine chlorohydrate. m.p. = 143-145° C.

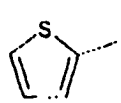
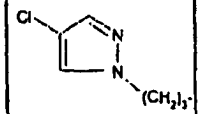
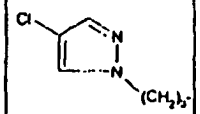
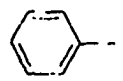
Example 13. Preparation of 4-methoxy-2-[4-(3-thienylcarbonyl)-1-piperazinyl] pyrimidine chlorohydrate.

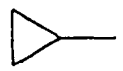
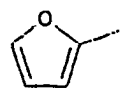
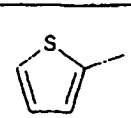
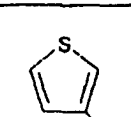
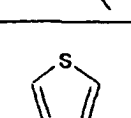
[0041] 0.8 g (2.63 mmol) of 4-methoxy-2-[4-(3-thienylcarbonyl)-1-piperazinyl] pyrimidine is dissolved in ethanol and a few drops of a solution of ethanol/hydrochloric acid are added, thus obtaining a precipitate which is filtered and dried, to yield 0.6 g (1.76 mmol) of 4-methoxy-2-[4-(3-thienylcarbonyl)-1-piperazinyl] pyrimidine chlorohydrate. m.p. = 154-156° C.

TABLE I

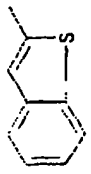
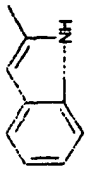


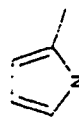
Example	R_1	R_2	X	Base or Salt	Procedure	m.p. (°C)	^{1}H RMN (MHz) (Solvent) δ	IR, cm^{-1}
1	CH_3O-		O	base	A	85-86	(300 MHz) ($CDCl_3$) 3.90 (broad singlet, 11H), 6.04 (d, J=5.5 Hz, 1H), 6.51 (dd, J= 3.5 Hz, J'= 1.7 Hz, 1H), 7.05 (d, J= 3.5 Hz, 1H), 7.51 (broad singlet, 1H), 8.07 (d, J= 5.5 Hz, 1H).	(KBr) 1623, 1598, 1583, 1561, 1502, 1439, 1264, 1025.
2	CH_3O-		O	HCl	D	162-164	(300 MHz) (DMSO-d_6) 3.83 (m, 4H), 3.91 (m, 4H), 3.95 (s, 3H), 6.36 (d, J= 6.3 Hz, 1H), 6.66 (m, 1H), 7.07 (m, 1H), 7.88 (m, 1H), 8.16 (d, J= 6.3 Hz, 1H).	(KBr) 2800-2200 (broad), 1642, 1605, 1483, 1262.
3	CH_3O-		O	base	B	71-73	(300 MHz) ($CDCl_3$) 3.83 (m, 4H), 3.89 (a.c., 7H,(δ= 3.89, s)), 6.04 (d, J= 5.7 Hz, 1H), 7.07 (dd, J= 5.1 Hz, J'= 3.9 Hz, 1H), 7.33 (d, J= 3.9 Hz, 1H), 7.48 (d, J= 5.1 Hz, 1H), 8.07 (d, J= 5.7 Hz, 1H).	(KBr) 1598, 1561, 1432, 1257, 989.

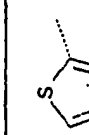
4	CH_3O-		O	HCl	D	143-145	(300 Mhz) (DMSO-d_6) 3.80 (m, 4H), 3.91 (m, 4H), 3.95 (s, 3H), 6.37 (d, J= 6.5 Hz, 1H), 7.15 (dd, J= 4.9 Hz, J'= 3.6 Hz, 1H), 7.49 (dd, J= 3.6 Hz, J' 1.2 Hz, 1H), 7.80 (dd, J= 4.9 Hz, J'= 1.2 Hz, 1H), 8.15 (d, J= 6.5 Hz, 1H).	(KBr) 2800-2200 (broad), 1637, 1614, 1597, 1484, 1437, 1409, 1210.
5	CH_3O-	CH_3	O	base	A	119-120	(300 MHz) ($CDCl_3$) 2.15 (s, 3H), 3.52 (m, 2H), 3.68 (m, 2H), 3.83 (m, 4H), 3.89 (s, 3H), 6.02 (d, J= 5.7 Hz, 1H), 8.06 (d, J= 5.7 Hz, 1H).	(KBr) 1654, 1595, 1561, 1423, 1345, 1249, 988.
6	CH_3O-		O	base	B	aceite	(300 MHz) ($CDCl_3$) 2.21 (m, 2H), 2.32 (m, 2H), 3.45 (m, 2H), 3.68 (m, 2H), 3.80 (m, 4H), 3.89 (s, 3H), 4.20 (t, J= 6.5 Hz, 2H), 6.03 (d, J= 5.7 Hz, 1H), 7.40 (s, 1H), 7.42 (s, 1H), 8.05 (d, J= 5.7 Hz, 1H).	(film) 1651, 1644, 1588, 1470, 1339.
7	CH_3O-		O	HCl	D	148-149	(300 MHz) (DMSO-d_6) 1.98 (q, J= 6.9 Hz, 2H), 2.33 (t, J= 7.0 Hz, 2H), 3.57 (m, 4H), 3.82 (m, 4H), 3.95 (s, 3H), 4.10 (t, J= 6.9 Hz, 2H), 6.36 (d, J=6.6 Hz, 1H), 7.50 (s, 1H), 7.98 (s, 1H), 8.14 (d, J= 6.6 Hz, 1H).	(KBr) 2800-2200 (broad), 1641, 1610, 1484, 1437, 1353, 1270, 1216.
8	CH_3O-		O	base	B	99-102	(300 MHz) ($CDCl_3$) 3.52 (m, 2H), 3.73-4.00 (a.c., 9H, (δ= 3.88, s)), 6.03 (d, J= 5.5 Hz, 1H), 7.44 (s, 5H), 8.06 (d, J= 5.5 Hz, 1H).	(KBr) 1625, 1606, 1597, 1558, 1461, 1428, 1266, 988.

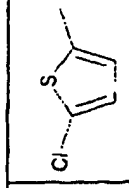
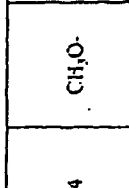
9	CH_3O-		O	base	B	76-78	(300 MHz) ($CDCl_3$) 0.80 (m, 2H), 1.02 (m, 2H), 1.78 (m, 1H), 3.68-3.92 (a.c., 11H, (δ= 3.89, s)), 6.02 (d, J= 5.7 Hz, 1H), 8.06 (d, J= 5.7 Hz, 1H).	(KBr) 1638, 1589, 1567, 1470, 1444, 1335, 1235, 1225.
10	CF_3-		O	base	A	112-113	(300 MHz) ($CDCl_3$) 3.84-4.00 (a.c., 8H), 6.51 (dd, J= 3.5 Hz, J'= 1.7 Hz, 1H), 6.82 (d, J= 4.8 Hz, 1H), 7.06 (dd, J= 3.5 Hz, J'= 1.0 Hz, 1H), 7.51 (dd, J= 1.7 Hz, J'= 1.0 Hz, 1H), 8.51 (d, J= 4.8 Hz, 1H).	(KBr) 1620, 1592, 1509, 1332, 1268, 1138.
11	CF_3-		O	base	B	136-137	(300 MHz) ($CDCl_3$) 3.86 (a.c., 4H), 3.96 (a.c., 4H), 6.82 (d, J= 4.8 Hz, 1H), 7.08 (dd, J= 5.0 Hz, J'= 3.7 Hz, 1H), 7.34 (dd, J= 3.7 Hz, J'= 1.1 Hz, 1H), 7.48 (dd, J= 5.0 Hz, J'= 1.1 Hz, 1H), 8.52 (d, J= 4.8 Hz, 1H).	(KBr) 1594, 1521, 1430, 1336, 1262, 1151.
12	CH_3O-		O	base	B	90-92	(300 MHz) ($CDCl_3$) 3.72 (m, 4H), 3.80-3.96 (a.c., 7H, (δ= 3.89, s)), 6.03 (d, J= 5.6 Hz, 1H), 7.22 (d, J= 5.0 Hz, 1H), 7.36 (m, 1H), 7.56 (broad singlet, 1H), 8.06 (d, J= 5.6 Hz, 1H).	(KBr) 1623, 1595, 1582, 1561.
13	CH_3O-		O	HCl	D	154-156	(300 MHz) (DMSO-d_6) 3.66 (m, 4H), 3.87 (m, 4H), 3.92 (s, 3H), 6.32 (d, J=6.1 Hz, 1H), 7.24 (m, 1H), 7.63 (broad singlet, 1H), 7.85 (broad singlet, 1H), 8.14 (d, J= 6.1 Hz, 1H).	(KBr) 2800-2200 (broad), 1642, 1617, 1598.

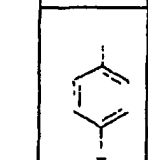
14	CH_3O-		O	base	B	90-92	(300 MHz) ($CDCl_3$) 2.51 (s, 3H), 3.79-3.93 (a.c., 11H, (δ= 3.89, s)), 6.03 (d, J= 5.6 Hz, 1H), 6.72 (m, 1H), 7.15 (d, J= 3.5 Hz, 1H), 8.06 (d, J= 5.6 Hz, 1H).	(KBr) 1625, 1590, 1562, 1510, 1471, 1414, 1261.
15	CH_3O-		O	HCl	D	115-119	(300 Mhz) ($CDCl_3$) 2.46 (s, 3H), 3.79 (m, 4H), 3.91 (m, 4H), 3.95 (s, 3H), 6.37 (d, J= 6.4 Hz, 1H), 6.84 (m, J = 3.6 Hz, 1H), 7.29 (d, J= 3.6 Hz, 1H), 8.14 (d, J= 6.4 Hz, 1H).	(KBr) 2800-2200 (broad), 1641, 1615, 1602, 1488, 1412, 1260.
16	CH_3O-		O	base	B	99-101	(300 MHz) ($CDCl_3$) 3.69 (a.c., 4H), 3.85-3.93 (a.c., 10H, (δ= 3.90, two singlets)), 6.02 (d, J= 5.7 Hz, 1H), 6.80 (d, J= 5.6 HZ, 1H), 7.37 (d, J= 5.6 Hz, 1H), 8.07 (d, J= 5.7 Hz, 1H).	(KBr) 1623, 1594, 1556.
17	CH_3O-		O	HCl	D	162-165	(300 MHz) (DMSO-d_6) 3.60 (a.c., 4H), 3.82-3.90 (a.c., 7H, (δ= 3.88, s)), 3.94 (s, 3H), 6.33 (d, J= 6.3 Hz, 1H), 7.04 (d, J= 5.6 Hz, 1H), 7.69 (d, J= 5.6 Hz, 1H), 8.14 (d, J= 6.3 Hz, 1H).	(KBr) 2800-2200 (broad), 1640, 1610, 1479, 1442, 1406.
18	CH_3O-		O	base	B	173-174	(300 MHz) ($CDCl_3$) 3.86 (m, 4H), 3.90 (s, 3H), 3.92 (m, 4H), 6.05 (d, J= 5.7 Hz, 1H), 7.42 (a.c., 2H), 7.53 (s, 1H), 7.85 (a.c., 2H), 8.07 (d, J= 5.7 Hz, 1H).	(KBr) 1604, 1589, 1559, 1459, 1259, 991.

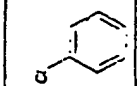
19	CH_3O-		O	HCl	D	155-156	(300 MHz) (DMSO-d_6) 3.84 (m, 4H), 3.89-3.97 (a.c., 7H, (δ= 3.93, s)), 6.32 (d, J= 6.3 Hz,1H), 7.45 (a.c., 2H), 7.81 (s, 1H), 7.94 (m, 1H), 8.02 (m, 1H), 8.15 (d, J= 6.3 Hz, 1H).	(KBr) 2800-2200 (broad), 1644, 1611, 1487
20	CH_3O-		O	base	B	202-203	(300 MHz) ($CDCl_3$) 3.92 (s, 3H), 3.93-4.10 (a.c., 8H), 6.05 (d, J= 5.6 Hz, 1H), 6.83 (d, J= 1.4 Hz, 1H), 7.15 (t, J= 7.3 Hz, 1H), 7.30 (t, J= 7.3 Hz, 1H), 7.45 (d, J= 8.3 Hz, 1H), 7.67 (d, J= 8.3 Hz, 1H), 8.09 (d, J= 5.6 Hz, 1H), 9.42 (broad singlet, 1H).	(KBr) 3260, 1605, 1578, 1571, 1438, 1336, 1251.
21	CH_3O-		O	base	B	175-176	(300 MHz) ($CDCl_3$) 3.59 (m, 2H), 3.88 (s, 3H), 3.92 (m, 6H), 6.04 (d, J= 5.6 Hz, 1H), 750 (a.c., 2H), 7.86 (a.c., 2H) 8.06 (d, J= 5.6 Hz, 1H).	(KBr) 1638, 1588, 1564, 1263.
22	CH_3O-		O	HCl	D	164-165	(300 MHz) (DMSO-d_6) 3.45-4.00 (a.c., 11H, (δ= 3.91, s)), 6.31 (d, J= 6.4 Hz, 1H), 7.60 (a.c., 2H), 7.88 (m, 1H), 8.12-8.18 (a.c., 2H. (δ=8.15, d, J= 6.4 Hz)).	(KBr) 2800-2200 (broad), 1640, 1629, 1625, 1609, 1418, 1219.
23	CH_3O-		O	base	B	142-143	(300 MHz) ($CDCl_3$) 3.90 (s, 3H), 3.92 (a.c., 8H), 6.03 (d, J= 5.6 Hz, 1H), 6.26 (m, 1H), 6.56 (m, 1H), 6.94 (m, 1H), 8.07 (d, J= 5.6 Hz, 1H), 9.87 (m, 1H).	(KBr) 3258, 1586, 1566, 1467, 1433.

24	CH_3O-		O	HCl	D	180-182 (dec)	(300 MHz) (DMSO-d_6) 3.86 (a.c., 4H). 3.94 (m, 4H). 3.97 (s. 3H). 6.13 (m. 1H). 6.41 (d. J= 6.7 Hz, 1H), 6.56 (m, 1H), 6.90 (m, 1H), 8.15 (d. J = 6.7 Hz, 1H), 11 52 (m, 1H).	(KBr) 3162. 2800-2200 (broad), 1630. 1605. 1487, 1428.
25	CH_3O-		O	base	B	69-71	(300 MHz) ($CDCl_3$) 3.57 (m, 2H). 3.72 (m, 4H). 3.80 (m, 2H), 3.88 (s, 3H), 3.97 (s. 2H), 6.02 (d, J= 5.7 Hz. 1H), 6.95 (m, 2H), 7.21 (m, 1H). 8.05 (d. J= 5.7 Hz, 1H).	(KBr) 1634, 1561, 1440, 1337, 1236.
26	CH_3O-		O	HCl	D	172-175	(300 MHz) (DMSO-d_6) 3.63 (m, 2H). 3.70 (m, 2H), 3.83 (m, 4H), 3.96 (s, 3H), 4.03 (s. 2H), 6.38 (d, J= 6.6 Hz, 1H), 6.96 (m, 2H), 7.39 (dd, J= 4.8 Hz, J= 1.7 Hz, 1H), 8.15 (d, J= 6.6 Hz, 1H).	(KBr) 2800-2200 (broad), 1667, 1636. 1606, 1411, 1216. 1208.
27	CH_3O-		O	base	B	87-89	(300 MHz) ($CDCl_3$) 2.29 (s, 3H), 3.68 (m, 4H). 3.86 (m, 4H), 3.88 (s, 3H), 6.03 (d. J= 5.6 Hz. 1H), 6.86 (d, J= 5.0 Hz, 1H), 7.30 (d, J= 5.0 Hz. 1H) 8.06 (d. J= 5.7 Hz, 1H).	(KBr) 1634, 1586, 1567, 1468, 1453, 1260.
28	CH_3O-		O	HCl	D	144-146	(300 MHz) (DMSO-d_6) 3.62 (m, 4H), 3.89 (m, 4H). 3.94 (s, 3H), 6.37 (d, J= 6.6 Hz, 1H), 6.95 (d, J= 4.9 Hz, 1H), 7.60 (d, J= 4.9 Hz, 1H), 8.14 (d, J= 6.6 Hz, 1H).	(KBr) 2800-2200 (broad), 1617. 1604, 1486, 1427. 1413, 1258.

29	CH_3O-		O	base	B	86-88	(300 MHz) ($CDCl_3$) 3.55-3.85 (a.c., 4H), 3.89 (s, 3H), 3.91 (m, 4H), 6.04 (d, J= 5.7 Hz, 1H), 6.94 (d, J= 5.1 Hz, 1H), 7.40 (d, J= 5.1 Hz, 1H), 8.07 (d, J= 5.7 Hz, 1H).	(KBr) 1622, 1587, 1561, 1509.
30	CH_3O-		O	HCl	D	144-147	(300 MHz) (DMSO-d_6) 3.50-3.70 (a.c., 4H), 3.87 (m, 4H), 3.91 (s, 3H), 6.31 (d, J= 6.2 Hz, 1H), 7.14 (d, J= 5.4 Hz, 1H), 7.85 (d, J= 5.4 Hz, 1H), 8.14 (d, J= 6.2 Hz, 1H).	(KBr) 2800-2200 (broad), 1636, 1608, 1481, 1443, 1407.
31	CH_3O-		O	base	B	229-231	(300 MHz) ($CDCl_3$) 3.80 (m, 4H), 3.84-3.93 (a.c., 7H, (δ= 3.88, s)), 6.03 (d, J= 5.7 Hz, 1H), 7.22 (m, 2H), 7.38 (m, 1H), 7.46 (d, J= 2.8 Hz, 1H), 7.73 (m, 1H), 8.07 (d, J= 5.7 Hz, 1H), 8.96 (broad singlet, 1H).	(KBr) 3181, 1610, 1590, 1559, 1467, 1339, 998.
32	CH_3O-		O	base	B	135-137	(300 MHz) ($CDCl_3$) 3.53 (m, 2H), 3.66 (m, 2H), 3.78 (a.c., 4H), 3.86 (s, 3H), 3.98 (s, 2H), 6.01 (d, J= 5.6 Hz, 1H), 7.26 (s, 1H), 7.40 (m, 2H), 7.85 (m, 2H), 8.03 (d, J= 5.6 Hz, 1H).	(KBr) 1619, 1590, 1561, 1553, 1454, 990.
33	CH_3O-		O	base	B	99-100	(300 MHz) ($CDCl_3$) 3.81 (m, 4H), 3.89 (m, 4H), 3.90 (s, 3H), 6.04 (d, J= 5.7 Hz, 1H), 6.89 (d, J= 4.0 Hz, 1H), 7.13 (d, J= 4.0 Hz, 1H), 8.07 (d, J= 5.7 Hz, 1H).	(KBr) 1610, 1594, 1584, 1561, 1442, 1258.

34	CH_3O-		O	HCl	D	159-162	(300 MHz) (DMSO-d_6) 3.80 (m, 4H), 3.91 (m, 4H), 3.94 (s, 3H), 6.35 (d, J= 6.3 Hz, 1H), 7.18 (d, J= 4.0 Hz, 1H), 7.40 (d, J= 4.0 Hz, 1H) 8.15 (d, J= 6.3 Hz, 1H).	(KBr) 2800-2200 (broad), 1639, 1613, 1592, 1436.
35	CH_3O-		O	base	B	127-129	(300 MHz) ($CDCl_3$) 3.58-3.96 (a.c., 14H, (δ= 3.84, s, y δ= 3.87, s)), 6.02 (d, J= 5.7 Hz, 1H), 6.92 (m, J= 8.8 Hz, 2H), 7.41 (m, J= 8.8 Hz, 2H), 8.05 (d, J= 5.7 Hz, 1H).	(KBr) 1624, 1587, 1562, 1433, 1252.
36	CH_3O-		O	HCl	D	162-164	(300 MHz) ($CDCl_3$) 3.76-3.88 (a.c., 7H, (δ= 3.85, s)), 3.93-4.36 (a.c., 7H, (δ= 4.07, s)), 6.29 (d, J= 6.8 Hz, 1H), 6.93 (d, J= 8.6 Hz, 2H), 7.40 (d, J= 8.6 Hz, 2H), 8.10 (d, J= 6.8 Hz, 1H).	(KBr) 2800-2200 (broad), 1631, 1615, 1484, 1428, 1413, 1260, 1244.
37	CH_3O-		O	base	B	123-126	(300 MHz) ($CDCl_3$) 3.37-4.03 (a.c., 11H, (δ= 3.89, s)), 6.04 (d, J= 5.7 Hz, 1H), 7.12 (m, J= 8.8 Hz, 2H), 7.46 (m, J= 8.8 Hz, J'= 5.4 Hz, 2H), 8.06 (d, J= 5.7 Hz, 1H).	(KBr) 1631, 1584, 1565, 1428, 1340, 1249.
38	CH_3O-		O	HCl	D	152-156	(300 MHz) ($CDCl_3$) 3.80 (m, 4H), 3.98-4.28 (a.c., 7H, (δ= 4.07, s)), 6.31 (d, J= 6.8 Hz, 1H), 7.13 (t, J= 8.6 Hz, 2H), 7.44 (dd, J= 8.6 Hz, J'= 5.3 Hz, 2H), 8.11 (d, J= 6.8 Hz, 1H).	(KBr) 2800-2200 (broad), 1630 (banda intensa), 1485, 1439, 1415, 1355, 1266, 1005.
39	CH_3O-		O	base	B	143-144	(300 MHz) ($CDCl_3$) 3.50 (m, 2H), 3.66-4.01 (a.c., 9H, (δ= 3.89, s)), 6.04 (d, J= 5.6 Hz, 1H), 7.40 (system AB, J= 8.7 Hz, 4H), 8.06 (d, J= 5.6 Hz, 1H).	(KBr) 1630, 1580, 1558, 1470, 1439, 1262.

40	CH_3O-		O	HCl	D	166-168	(300 MHz) ($CDCl_3$) 3.80 (m, 4H), 3.97-4.38 (a.c., 7H, (δ= 4.09, s)), 6.32 (d, J= 6.9 Hz, 1H), 7.37 and 7.43 (system AB, J= 8.6 Hz, 4H), 8.11 (d, J= 6.9 Hz, 1H).	(KBr) 2800-2200 (broad), 1631, 1609, 1492, 1431, 1420,1359, 1262.
41	CH_3O-		O	base	B	78-81	(300 MHz) ($CDCl_3$) 3.50 (m, 2H), 3.66-4.02 (a.c., 1211,(δ= 3.83, s y δ= 3.88, s)). 6.03 (d, J= 5.6 Hz, 1H), 6.99 (a.c., 3H), 7.33 (t, J= 8.0 Hz, 1H), 8.06 (d, J= 5.6 Hz, 1H).	(KBr) 1630, 1584, 1562, 1430, 1338, 1236.
42	CH_3O-		O	HCl	D	158-161	(300 MHz) ($CDCl_3$) 3.61-4.38 (a.c., 14H, (δ= 3.83, s and δ= 4.08, s)), 6.30 (d, J= 6.9 Hz, 1H), 6.96 (a.c., 3H), 7.34 (t, J= 8.1 Hz, 1H), 8.10 (d, J= 6.9 Hz, 1H),	(KBr) 2800-2200 (broad), 1636, 1605, 1490, 1418, 1270.
43	CH_3O-		O	base	B	106-107	(300 MHz) ($CDCl_3$) 3.49 (m, 2H), 3.66-4.02 (a.c., 9H, (δ= 3.89, s)), 6.04 (d, J= 5.6 Hz, 1H), 7.19 (a.c., 3H), 7.41 (m, 1H), 8.06 (d, J= 5.6 Hz, 1H).	(KBr) 1639, 1593, 1582, 1459, 1439, 1342.
44	CH_3O-		O	HCl	D	153-156	(300 MHz) ($CDCl_3$) 3.56-4.43 (a.c., 11H, (δ= 4.09, s)), 6.32 (d, J= 6.9 Hz, 1H), 7.18 (a.c., 3H), 7.43 (m, 1H), 8.11 (d, J= 6.9 Hz, 1H).	(KBr) 2800-2200 (broad), 1639, 1610, 1489, 1415, 1288, 1266.

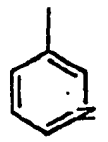
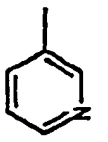
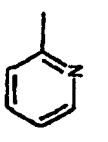
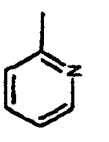
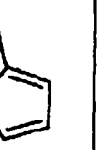
45	CH_3O-		O	base	B	94-96	(300 MHz) ($CDCl_3$) 3.49 (m, 2H), 3.70-4.00 (a.c., 9H, δ= 3.89, s)), 6.04 (d, J= 5.7 Hz, 1H), 7.29-7.45 (a.c., 4H), 8.07 (d, J= 5.7 Hz, 1H).	(KBr) 1645, 1593, 1561, 1433, 1256.
46	CH_3O-		O	HCl	D	166-170	(300 MHz) ($CDCl_3$) 3.60-3.97 (a.c., 4H), 3.98-4.37 (a.c., 7H, (δ= 4.08, s)), 6.31 (d, J= 7.0 Hz, 1H), 7.29 (m, 1H), 7.42 (a.c., 3H), 8.11 (d, J= 7.0 Hz, 1H).	(KBr) 2800-2200 (broad), 1632, 1611, 1597, 1488, 1414, 1286.
47	CH_3O-		O	base	B	113-115	(300 MHz) ($CDCl_3$) 3.33 (m, 2H), 3.72-3.99 (a.c., 12H, (δ= 3.84, s y δ= 3.88, s)), 6.02 (d, J= 5.6 Hz, 1H), 6.93 (d, J= 8.6 Hz, 1H), 7.02 (m, 1H), 7.28 (m, 1H), 7.38 (m, 1H), 8.05 (d, J= 5.6 Hz, 1H).	(KBr) 1619, 1584, 1562, 1241.
48	CH_3O-		O	HCl	D	163-164	(300 MHz) ($CDCl_3$) 3.51 (m, 2H), 3.75-4.33 (a.c., 12 H, (δ= 3.85, s and δ= 4.09, s)), 6.28 (d, J= 7.0 Hz, 1H), 6.95 (d, J= 8.3 Hz, 1H), 7.02 (m, 1H), 7.25 (m, 1H), 7.40 (m, 1H), 8.10 (d, J= 8.3 Hz, 1H).	(KBr) 2800-2200 (broad), 1644, 1628, 1611, 1490, 1261.
49	CH_3O-		O	base	B	102-103	(300 MHz) ($CDCl_3$) 3.40 (broad, 2H), 3.77-3.98 (a.c., 9H, (δ= 3.89, s)), 6.03 (d, J= 5.6 Hz, 1H), 7.12 (m, 1H), 7.23 (m, 1H), 7.42 (m, 2H), 8.06 (d, J= 5.6 Hz, 1H).	(KBr) 1641, 1595, 1561, 1466.
50	CH_3O-		O	HCl	D	148-152	(300 MHz) ($CDCl_3$) 3.58 (broad, 2H), 3.82-4.39 (a.c., 9H, (δ= 4.08, s)), 6.31 (d, J= 6.9 Hz, 1H), 7.13 (m, 1H), 7.25 (m, 1H), 7.44 (m, 2H), 8.11 (d, J= 6.9 Hz, 1H).	(KBr) 2800-2200 (broad), 1643, 1612, 1490, 1430, 1418, 1287, 1260.

51	CH_3O-		O	base	B	112-115	(300 MHz) ($CDCl_3$) 3.32 (m, 2H), 3.71-4.00 (a.c., 9H, (δ= 3.88, s)), 6.03 (d, J= 5.6 Hz, 1H), 7.30-7.46 (a.c., 4H), 8.06 (d, J= 5.6 Hz, 1H).	(KBr) 1640, 1593, 1561.
52	CH_3O-		O	HCl	D	152-154	(300 MHz) ($CDCl_3$) 3.49 (m, 2H), 3.73-4.40 (a.c., 9H, (δ= 4.08, s)), 6.30 (d, J= 6.7 Hz, 1H), 7.25-7.48 (a.c., 4H), 8.10 (d, J= 6.7 Hz, 1H).	(KBr) 2800-2200 (broad), 1643, 1609, 1492, 1431, 1415, 1288, 1258.
53	CH_3O-		O	base	B	90-91	(300 MHz) ($CDCl_3$) 1.82-2.13 (a.c., 3H), 2.31 (m, 1H), 3.58 (m, 2H), 3.67-3.82 (a.c., 4H), 3.82-3.98 (a.c., 7H, (δ= 3.87, s)), 4.63 (dd, J= 7.4 Hz, J'= 5.3 Hz, 1H), 6.00 (d, J= 5.6 Hz, 1H), 8.03 (d, J= 5.6 Hz, 1H)	(KBr) 1653, 1596, 1586, 1564, 1505, 1239, 987.
54	CH_3O-		S	base	C	125-129	(300 MHz) ($CDCl_3$) 3.68 (m, 2H), 3.82 (m, 2H), 3.88 (s,3H), 4.07 (m, 2H), 4.48 (m, 2H), 6.06 (d, J= 5.7 Hz, 1H), 7.29-7.41 (a.c., 5H), 8.08 (d, J= 5.7 Hz, 1H).	(KBr) 1589, 1561, 1470, 1233.

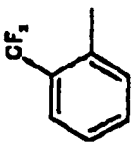
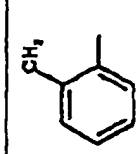
Example	R_1	R_2	X	Base or Salt	Procedure	m.p. (°C)	^{1}H RMN (MHz) (Solvent) δ	IR cm^{-1}
55	CH_3O-		O	HCl	D	149-151	(300 MHz) ($CDCl_3$) 1.84-2.14 (a.c., 2H), 2.30 (m, 1H) , 3.41-4.53 (a.c., 13H, (δ=4.06. s)), 4.57 (t. J=6.3 Hz, 1H), 6.29 (d, J=6.9 Hz. 1H). 8.12 (d, J=6.9 Hz, 1H).	(KBr) 2800-2200 (broad) , 1644, 1609. 1491. 1241. 1217.
56	CH_3O-		S	HCl	D	151-154	(300 MHz) ($CDCl_3$) 3.87 (broad, 2H), 4.09 (s,3H), 4.22 (broad, 4H), 4.53 (broad. 2H), 6.33 (d, J=6.2 Hz, 1H). 7.27-7.44 (a.c., 5H), 8.12 (d, J=6.2 Hz, 1H).	(KBr) 2800-2200 (broad) 1637, 1604. 1494. 1212.
57	CH_3O-		O	HCl	D	136-138	(300 Mhz) ($CDCl_3$) 3.61-4.37 (a.c., 11H. (δ=4.08. s)). 6.30 (d, J= 7.2 Hz, 1H), 7.43 (m. 5H), 8.10 (d. J=7.2 Hz, 1H).	(KBr) 2800-2200 (broad). 1643, 1637, 1629. 1611, 1488, 1265.

58	CH_3O-		O	base	B	123-126	(300 MHz) ($CDCl_3$) 3.45 /m, 2H), 3.74-3.99 (a.c., 9H, (δ=3.88, s)), 6.04 (d, J=5 6 Hz, 1H), 7.56 and 7.71 (system AB, J=8.0 Hz, 4H), 8.06 (d, J 5.6 Hz, 1H).	(KBr) 1645, 1593, 1561, 1433, 1256.
59	CH_3O-		O	HCl	D	140-143	(300 MHz) ($CDCl_3$) 3.57-4.29 (a.c., 11H, (δ=4.08, s)), 7.31 (d, J= 6.7 Hz, 1H), 7.55 and 7.73 (system AB, J= 8.2 Hz, 4H), 8.11 (d, J=6.7 Hz, 1H).	(KBr) 2800-2200 (broad), 1640, 1611, 1491, 1327, 1264.
60	CH_3O-		O	base	B	oil	(300 MHz) ($CDCl_3$)) 3.49 (m, 2H), 3.73- 4.00 (a.c., 9H, (δ=3.88, s)), 6.04 (d, J =5.6 Hz, 1H), 7.53-7.78 (a.c., 4H), 8.06 (d, J= 5.6 Hz, 1H).	(film) 1643, 1587, 1567, 1332.
61	CH_3O-		O	HCl	D	177-179	(300 MHz) ($CDCl_3$) 3.55-4.40 (a.c. 1111, (δ=4.08. s)), 6.32 (d, J= 7.1 Hz, 1H), 7.60 (m, 2H), 7.72 (m, 2H), 8.11 (d, J= 7.1 Hz, 1H).	(KBr) 2800-2200 (broad), 1637, 1611, 1490, 1333, 1322, 1264.
62	CH_3O-		O	base	B	93-97	(300 MHz) ($CDCl_3$) 3.24 (m, 2H), 3.75 (m, 2H), 3.82-3.96 (a.c., 7H, (δ=3.87, s)), 6.03 (d, J= 5.6 Hz, 1H), 7.36 (d, J= 7.3 Hz, 1H), 7.54 (t, J=7.6 Hz, 1H), 7.62 (t, J= 7.6 Hz, 1H), 7.73 (d, J= 7.3 Hz, 1H), 8.05 (d, J= 5.6 Hz, 1H).	(KBr) 1641, 1587, 1569, 1436, 1341, 1314, 1251
63	CH_3O-		O	HCl	D	155-158	(300 MHz) ($CDCl_3$) 3.42 (broad singlet, 2H), 3.70-4.43 (a.c., 9H, (δ=4.07. s)), 6.30 (d, J= 7.1 Hz, 1H), 7.33 (d, J= 7.2 Hz, 1H), 7.60 (m, 2H), 7.74 (d, J= 7.2 Hz, 1H), 8.08 (d, J= 7.1 Hz, 1H).	(KBr) 2800-2200 (banda ancha), 1645, 1604, 1486, 1317, 1126.

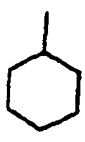
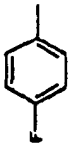
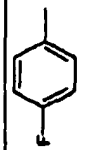
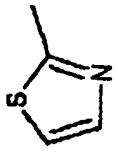
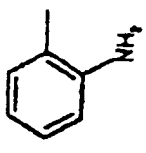
64	CH_3O-		O	base	B	102-105	(300 MHz) ($CDCl_3$) 3.51 (m, 2H), 3.69-4.00 (a.c., 9H, (=3.88,s)), 6.04 (d, J= 5.6 Hz, 1H), 7.39 (dd, J= 7.7 Hz, J'=5.0 Hz, 1H), 7.79 (d, J= 7.7 Hz, 1H), 8.06 (d, J= 5.6 Hz, 1H), 8.70 (m, 2H).	(KBr) 1623, 1589, 1566,1439.
65	CH_3O-		O	2 HCl	D	148-151	(300 MHz) (DMSO-d_6) 3.66-4.42 (a.c., 11H, (δ=3.92, s)), 6.32 (d, J= 6.3 Hz, 1H), 7.78 (dd, J= 7.9 Hz, J'= 5.4 Hz, 1H), 8.14 (d, J= 6.3 Hz, 1H), 8.22 (d, J= 7.9 Hz, 1H), 8.81 (d, J= 5.4 Hz, 1H), 8.85 (s, 1H).	(KBr) 2800-2200 (broad), 1641, 1609, 1493, 1442, 1268
66	CH_3O-		O	base	B	149-152	(300 MHz) ($CDCl_3$) 3.43 (m, 2H), 3.75-3.98 (a.c., 9H, (δ=3.88,s)), 6.05 (d, J= 5.7 Hz, 1H), 7.32 (m, 2H), 8.06 (d, J= 5,7 Hz, 1H), 8.73 (m, 2H).	(KBr) 1638, 1589, 1561, 1340.
67	CH_3O-		O	2 HCl	D	157-161	(300 MHz) (DMSO-d_6) 3.42 (m, 2H), 3.73-4.05 (a.c., 9H, (δ=3.94, s)), 6.37 (d, J= 6.5 Hz, 1H), 7.98 (d, J= 5.5 Hz, 2H), 8.14 (d, J= 6.5 Hz, 1H), 8.96 (d, J= 5.5 Hz, 1H).	(KBr) 2800-2200 (broad), 1634, 1610, 1488, 1415, 1356, 1287, 1265.
68	CH_3O-		O	base	B	127-131	(300 MHz) ($CDCl_3$) 3.68 (m, 4H), 3.89 (s, 3H), 3.92 (m, 4H), 6.06 (d, J = 5.7 Hz, 1H), 7.12 (s, 1H), 7.24 (s, 1H), 7.91 (s, 1H), 8.07 (d, J= 5.7 Hz, 1H).	(KBr) 1691, 1599, 1556, 1430, 1418, 1241, 988
69	CH_3O-		O	HCl	D	160-163	(300 MHz) (DMSO-d_6) 3.68 (m, 4H), 3.95 (s, 3H), 3.98 (m, 4H), 6.35 (d, J= 6.0 Hz, 1H), 7.82 (s, 1H), 8.05 (s, 1H), 8.17 (d, J= 6,0 Hz, 1H), 9.54 (s, 1H).	(KBr) 2800-2200 (broad), 1733, 1639, 1612, 1490, 1416

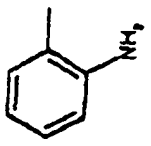
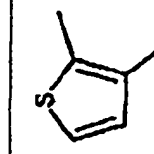
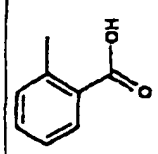
70	CF_3-		O	base	B	125-126	(300 MHz) (CDCl$_3$) 3.41-4.15 (a.c., 8H), 6.84 (d, J=4.8 Hz, 1H), 7.40 (dddd, J=7.9 Hz, J= 4.8 Hz, J= 0.9 Hz, 1H), 7.80 (ddd, J= 7.9 Hz, J= 2.1 Hz, J= 1.8 Hz, 1H), 8.53 (d, J= 4.8 Hz, 1H), 8.71 (m, 2H).	(KBr) 1631, 1593, 1502, 1434, 1331, 1257, 1158.
71	CF_3-		O	HCl	D	149-154	(300 MHz) (DMSO-d_6, TFA) 3.46 (m, 2H), 3.67-4.03 (a.c., 6H), 7.03 (d, J= 4.8 Hz, 1H), 8.05 (dd, J= 8.0 Hz, J= 5.6 Hz, 1H), 8.56 (d, J= 8.0 Hz, 1H), 8.68 (d, J= 4.8 Hz, 1H), 8.95 (d, J= 5.6 Hz, 1H), 9.04 (s, 1H).	(KBr) 2800-2200 (broad), 1634, 1595, 1524, 1435, 1273, 1186, 981.
72	CH_3O-		O	base	B	108-111	(300 MHz) (CDCl$_3$) 3.69 (m, 2H), 3.81-4.02 (a.c., 9H, (δ= 3.88, s)), 6.02 (d, J= 5.7 Hz, 1H), 7.37 (m, 1H), 7.70 (d, J= 8.0 Hz, 1H), 7.82 (dd, J= 8.0 Hz, J= 1.7 Hz, 1H), 8.06 (d, J= 5.7 Hz, 1H), 8.61 (d, J= 5.1 Hz, 1H).	(KBr) 1623, 1595, 1585, 1565, 1473, 1263.
73	CH_3O-		O	2HCl	D	157-161	(300 MHz) (DMSO-d_6, TFA) 3.67 (broad), 3.79-4.07 (a.c., 9H, (δ=3.99, s)), 6.48 (d, J= 6.5 Hz, 1H), 7.63 (m, 1H), 7.78 (m, 1H), 8.09 (m, 1H), 8.19 (d, J= 6.5 Hz, 1H), 8.68 (d, J= 4.6 Hz, 1H).	(KBr) 2800-2200 (broad), 1650, 1606, 1495, 1444, 1265
74	C_6H_5O-		O	base	B	97-99	(300 MHz) (CDCl$_3$) 1.37 (t, J= 7.1 Hz, 3H), 3.77-3.93 (a.c., 8H), 4.33 (q, J= 7.1 Hz, 2H), 6.01 (d, J= 5.6 Hz, 1H), 7.07 (m, 1H), 7.33 (d, J= 3.4 Hz, 1H), 7.47 (d, J= 4.9 Hz, 1H), 8.06 (d, J=5.6 Hz, 1H).	(KBr) 1605, 1583, 1560, 1449, 1438, 1258, 1237.

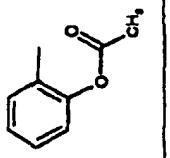
75	C_3H_5O-		O	HCl	D	138-139	(300 MHz) ($CDCl_3$) 1.45 (t, J=7.1 Hz, 3H), 3.80-4.40 (a.c., 4H), 4.50 (q, J= 7.1 Hz, 2H), 6.27 (d, J= 6.9 Hz, 1H), 7.08 (dd, J = 4.9 Hz, J= 3.8 Hz, 1H), 7.33 (d, J= 3.8 Hz, 1H), 7.50 (d, J= 4.9 Hz, 1H), 8.10 (d, J= 6.9 Hz, 1H).	(KBr) 2800-2200 (broad), 1609, 1434, 1257, 994
76	C_3H_5O-		O	base	B	91-94	(300 MHz) ($CDCl_3$) 1.36 (t, J= 7.1 Hz, 3H), 3.45-3.97 (a.c., 8H). 4.32 (q, J= 7.1 Hz, 2H), 6.01 (d, J= 5.6 Hz, 1H), 6.93 (d, J= 5.2 Hz, 1H), 7.40 (d, J=5.2 Hz, 1H), 8.06 (d, J=5.6 Hz, 1H).	(KBr) 1625, 1558, 1436, 1255
77	C_3H_5O-		O	HCl	D	167-169	(300 MHz) ($CDCl_3$) 1.46 (t, J= 7.0 Hz, 3H), 3.81 (broad, 4H), 3.93-4.42 (a.c., 4H), 4.51 (q, J= 7.0 Hz, 2H), 6.28 (d, J=6.9 Hz, 1H), 6.95 (d, J=5.3 Hz, 1H). 7.44 (d, J= 5.3 Hz, 1H), 8.10 (d, J= 6.9 Hz, 1H).	(KBr) 2800-2200 (broad) 1639, 1617, 1604, 1460, 1440, 1292, 1260, 1203.
78	C_3H_5O-		O	base	B	99-101	(300 MHz) ($CDCl_3$) 1.36 (t, J= 7.1 Hz, 3H), 3.23 (m, 2H), 3.73 (m, 2H), 3.88 (a.c., 4H), 4.31 (q, J= 7.1 Hz, 2H), 6.00 (d, J= 5.6 Hz, 1H), 7.36 (d, J= 7.2 Hz, 1H), 7.54 (m, 1H), 7.62 (m, 1H), 7.73 (m, 1H), 8.05 (d, J= 5.6 Hz, 1H).	(KBr) 1624, 1582, 1437, 1258

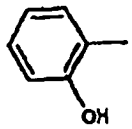
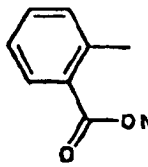
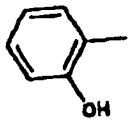
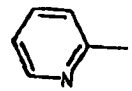
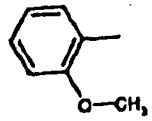
79	C_2H_5O-		O	HCl	D	146-148	(300 MHz) ($CDCl_3$) 1.45 (t, J= 7.1 Hz, 3H), 3.42 (broad, 2H), 3.68-4.41 (a.c., 6H), 4.50 (m, 2H), 6.27 (d, J= 6.7 Hz, 1H), 7.33 (d, J=7.1 Hz, 1H), 7.61 (m, 2H), 7.74 (d, J= 7.9 Hz, 1H), 8.07 (d, J=6.7 Hz, 1H).	(KBr) 2800-2200 (broad), 1640, 1602, 1437, 1320, 1259
80	CH_3O-		O	base	B	70-73	(300 MHz) ($CDCl_3$) 2.33 (s, 3H), 3.30 (broad, 2H), 3.74 (broad, 2H), 3.83-3.98 (a.c., 7H, (δ=3.87, s)), 6.03 (d, J= 5.5 Hz, 1H), 7.15-7.34 (m, 4H), 8.05 (d, J= 5.5 Hz, 1H).	(KBr) 1621, 1598, 1559, 1430, 1263
81	CH_3O-		O	HCl	D	151-153	(300 MHz) ($CDCl_3$) 2.30 (s, 3H), 3.48 (broad, 2H), 3.90-4.35 (a.c., 9H, (=4.08, s)), 6.29 (d, J= 6.0 Hz, 1H), 7.13-7.32 (a.c., 4H), 8.10 (d, J= 6.0 Hz, 1H).	(KBr) 2800-2200 (broad), 1643, 1630, 1610, 1491, 1415, 1263
82	$(CH_3)_2CHO$		O	base	B	112-115	(300 MHz) ($CDCl_3$) 1.31 (d, J= 6.0 Hz, 6H), 3.40-4.00 (a.c., 8H), 5.24 (h, J= 6.0 Hz, 1H), 5.96 (d, J= 5.7 Hz, 1H), 7.13 (t, J= 7.8 Hz, 2H), 7.46 (m, J= 8.8 Hz, J'= 5.4 Hz, 2H), 8.03 (d, J= 5.7 Hz, 1H).	(KBr) 1632, 1583, 1557, 1450, 1236
83	$(CH_3)_2CHO$		O	HCl	D	163-166	(300 MHz) ($CDCl_3$) 1.41 (d, J= 6.0 Hz, 6H), 3.65-4.40 (a.c., 8H), 5.39 (m, 1H), 6.22 (d, J= 6.9 Hz, 1H), 7.13 (m, 2H), 7.43 (m, 2H), 8.07 (d, J=6.9 Hz, 1H).	(KBr) 2800-2200 (broad) 1636, 1608, 1458, 1432, 1259

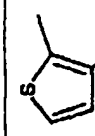
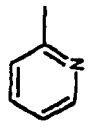
84	$(CH_3)_2CHO$		O	base	B	---	(300 MHz) ($CDCl_3$) 1.29 (d, J= 6.0 Hz, 6H), 3.24 (m, 2H), 3.72 (m, 2H), 3.89 (m, 4H), 5.24 (h, J= 6.0 Hz, 1H), 5.97 (d, J=5.7 Hz, 1H), 7.36 (d, J= 7.2 Hz, 1H), 7.58 (m, 2H), 7.73 (d, J= 7.8 Hz, 1H), 8.04 (d, J= 5.7 Hz, 1H).	(KBr) 1651, 1581, 1563, 1317
85	$(CH_3)_2CHO$		O	HCl	D	159-161	(300 MHz) ($CDCl_3$) 1.42 (d, J=5.6 Hz, 6H), 3.43 (broad, 2H), 3.67-4.44 (a.c., 6H), 5.40 (m, 1H), 6.22 (d, J= 6.8 Hz, 1H), 7.33 (d, J= 6.9 Hz, 1H), 7.61 (m, 2H), 7.75 (d, J= 7.5 Hz, 1H), 8.05 (d, J= 6.9 Hz, 1H).	(KBr) 2800-2200 (broad), 1640, 1604, 1473, 1317, 1122
86	$(CH_3)_2CHO$		O	base	B	68-70	(300 MHz) ($CDCl_3$) 1.33 (d, J= 6.1 Hz, 6H), 3.40-4.07 (a.c., 8H), 5.26 (h, J= 6.1 Hz, 1H), 5.97 (d, J= 5.7 Hz, 1H), 6.93 (d, J= 5.3 Hz, 1H), 7.39 (d, J= 5.3 Hz, 1H), 8.05 (d, J = 5.7 Hz, 1H).	(KBr) 1631, 1583, 1557, 1445
87	$(CH_3)_2CHO$		O	HCl	D	148-150	(300 MHz) ($CDCl_3$) 1.42 (d, J= 6.1 Hz, 6H), 3.66-4.44 (a.c., 8H), 5.39 (h, J= 6.1 Hz, 1H), 6.23 (d, J= 5.7 Hz, 1H), 6.95 (d, J= 5.3 Hz, 1H), 7.44 (d, J= 5.3 Hz, 1H), 8.08 (d, J= 5.7 Hz, 1H).	(KBr) 2800-2200 (broad) 1644, 1612, 1462, 1446, 1313, 1282, 1250
88	CH_3O-		O	base	B	109-111	(300 MHz) ($CDCl_3$) 1.28 (m, 3H), 1.46-1.89 (a.c., 7H), 2.50 (t, J= 11.2 Hz, J= 3.3 Hz, 1H), 3.56 (m, 2H), 3.69 (m, 2H), 3.81 (m, 4H), 3.89 (s, 3H), 6.02 (d, J= 5.5 Hz, 1H), 8.06 (d, J=5.5 Hz, 1H).	(KBr) 1629, 1591, 1556, 1339, 1239, 992

89	CH_3O-		O	HCl	D	121-124	(300 MHz) ($CDCl_3$) 1.27 (m, 3H), 1.53 (m, 2H), 1.75 (a.c., 5H), 2.47 (m, 1H), 3.75 (broad singlet, 4H), 3.92 (m, 2H), 4.07 (s, 3H), 4.29 (m, 2H), 6.30 (d, J= 7.0 Hz, 1H), 8.11 (d, J= 7.0 Hz, 1H).	(KBr) 2800-2200 (broad), 1632, 1604, 1487, 1431, 1212
90	C_2H_5O-		O	base	B	136-138	(300 MHz) ($CDCl_3$) 1.37 (t, J= 7.0 Hz, 3H), 3.38-4.00 (a.c., 8H), 4.32 (q, J= 7.0 Hz, 2H), 6.01 (d, J= 5.7 Hz, 1H), 7.12 (t, J= 8.5 Hz, 2H), 7.45 (m, 2H), 8.06 (d, J= 5.7 Hz, 1H).	(KBr) 1616, 1590, 1557, 1432
91	C_2H_5O-		O	HCl	D	155-157	(300 MHz) ($CDCl_3$) 1.46 (t, J= 7.0 Hz, 3H), 3.67-4.38 (a.c., 8H), 4.51 (q, J= 7.0 Hz, 2H), 6.28 (d, J= 6.8 Hz, 1H), 7.14 (t, J= 8.8 Hz, 2H), 7.45 (m, 2H), 8.11 (d, J= 6.8 Hz, 1H).	(KBr) 2800-2200 (broad), 1636, 1606, 1458, 1436, 1258
92	CH_3O-		O	base	B	106-108	(300 MHz) ($CDCl_3$) 3.85-3.99 (a.c., 9H, (δ=3.90, s)), 4.50 (m, 2H), 6.03 (d, J= 5.7 Hz, 1H), 7.56 (d, J= 3.2 Hz, 1H), 7.91 (d, J= 3.2 Hz, 1H), 8.07 (d, J= 5.7 Hz, 1H)	(KBr) 1596, 1565, 1496, 1442, 1257, 1004
93	CH_3O-		O	base	B	145-147	(300 MHz) ($CDCl_3$) 3.70 (broad, 4H), 3.83-3.90 (a.c., 7H, (δ=3.88, s)), 4.35 (s, 2H), 6.03 (d, J= 5.6 Hz, 1H), 6.74 (m, 2H), 7.11 (m, 1H), 8.06 (d, J= 5.6 Hz, 1H).	(KBr) 3444, 3323, 1617, 1586, 1498, 1467, 1260

94	CH_3O-		O	2 HCl	D	155-157	(300 MHz) (DMSO-d$_6$) 3.61 (broad, 4H), 3.94 (s, 7H), 6.37 (d, J= 6.5 Hz, 1H), 7.10 (t, J= 7.5 Hz, 1H), 7.20 (d, J= 7.5 Hz, 1H), 7.32 (d, J= 7.5 Hz, 1H), 7.38 (t, J= 7.5 Hz. 1H), 8.14 (d, J= 6.5 Hz, 1H).	(KBr) 3700-2200 (broad), 1614, 1493, 1439, 1257.
95	CH_3O-		O	base	B	oil	(300 MHz) (CDCl$_3$) 3.73 (broad, 4H), 3.86-3.99 (a.c., 7H, (δ=3.89,s)), 6.03 (d, J= 5.7 Hz, 1H), 6.78 (d, J= 5.4 Hz, 1H), 7.37 (dd, J= 5.4 Hz, J= 3.7 Hz, 1H), 8.06 (d, J= 5.7 Hz, 1H).	(KBr) 1626, 1586, 1469, 1443
96	CH_3O-		O	HCl	D	156-157	(300 MHz) (CDCl$_3$) 3.86 (broad singlet, 4H), 4.08 (s, 5H), 4.23-4.45 (m, 2H), 6.31 (d, J= 6.9 Hz. 1H), 6.80 (d, J=5.5 Hz. 1H), 7.41 (dd, J= 5.5 Hz, J= 3.7 Hz, 1H), 8.12 (d, J= 6.9 Hz, 1H).	(KBr) 2800-2200 (broad), 1618, 1482, 1413, 1262, 995
97	CH_3O-		O	---	B	186-188	(300 MHz) (CDCl$_3$) 3.25 (m, 2H), 3.65-3.99 (a.c., 9H, (δ=3.86,s)), 6.02 (d, J= 5.8 Hz, 1H), 7.30 (d, J= 7.6 Hz, 1H), 7.45 (t, J= 7.6 Hz, 1H . 7.57 (t, J= 7.6 Hz, 1H), 8.06 (m, 2H).	(KBr) 3600-2500 (broad), 1711, 1583, 1444, 1342, 1266

98	CH_3O-		0	base	B	139-142	(300 Mhz) (CDCl$_3$) 2.27 (s, 3H), 3.38 (m, 2H), 3.74-3.94 (a.c., 9H, (=1,87, s)), 6.03 (d, J= 5.7 Hz, 1H), 7.18 (d, J= 8.2 Hz, 1H), 7.32 (m, 2H), 7.44 (m, 1H), 8.05 (d, J= 5.7 Hz, 1H)	(KBr) 1764, 1637, 1566, 1429, 1338, 1259, 1194

99	CH_3O-		O	base	B	186-188	(300 MHz) ($CDCl_3$) 3.80 (m, 4H), 3.86-3.95 (a.c., 7H), (δ=3.89)), 6.04 (d, J=5,7 Hz, 1H), 6.87 (t, J=7.5 Hz, 1H), 7.03 (d, J=8.1 Hz, 1H), 7.28 (m, 1H), 7.35 (m, 1H), 8.06 (d, J=5.7 Hz, 1H).	KBr (3500-2500 (broad), 1566, 1443, 1335, 1229.
100	CH_3O-		O	---	D	---	(300 MHz) (DMSO-d_6) 3.06 (m, 2H), 3.38-3.72 (a.c., 4H), 3.79 (s, 3H), 3.92 (m, 2H), 6.04 (d, J=5.4 Hz, 1H), 7.02 (m, 1H), 7.27 (m, 2H), 7.79 (m, 1H), 8.06 (d, J=5,4 Hz, 1H).	(KBR) 1624, 1588, 1563, 1382.
101	CH_3O-		O	HCl	D	158-159	(300 MHz) (DMSO-d_6) 3.34 (m, 2H), 3.62-4.01 (a.c., 9H, (δ=3.93)), 6.36 (d, J=6.3 Hz, 1H), 6.84 (t, J=7.2 Hz, 1H), 6.91 (d, J=8.1 Hz, 1H), 7.15 (m, 1H), 7.23 (m, 1H), 8.13 (d, J=6.3 Hz, 1H).	(KBr) 3500-2500 (broad), 1622, 1493, 1361,1289, 1211.
102	CH_3O-		O	HCl	D	151-153	(300 MHz) ($CDCl_3$) 3.93 (broad s, 4H), 4.00-4.40 (a.c., 7H, (δ=4.07, s)), 6.29 (d, J=6.8 Hz, 1H), 7.40 (m, 1H), 7 72 (broad d, J=7.2 Hz, 1H), 7.84 (dt, J=7.6 Hz, J'=1.7 Hz, 1H), 8.11 (d, J=6.8 Hz, 1H), 8.59 (d, J=5.0 Hz, 1H).	(KBr) 3500-2500 (broad), 1616, 1486, 1413, 1311, 1212.
103	CH_3O-		O	NO_3H	D	137-139	(300 MHz) ($CDCl_3$) 3.31-3.64 (a.c., 2H), 3.70-4.24 (a.c., 12H, (δ=3.85, s)(δ=4.08, s)), 6.30 (d, J=6.9 Hz, 1H), 6.95 (8.2 Hz, 1H), 8.23 (d, J=6.9 Hz, 1H).	(KBr) 3500-2500 (broad), 1646, 1485, 1281, 1000, 750.

104	CH_3O-		O	NO_3H	D	129-131	(300 Mhz) ($CDCl_3$) 3.81 (broad, 4H), 4.02 (broad, 4H), 4.08 (s, 3H), 6.33 (d, J= 7.0 Hz, 1H), 6.95 (d, J= 5.0 Hz, 1H), 8.25 (d, J= 7.0 Hz, 1H)	(KBr) 3500-2500 (broad), 1643, 1486, 1411, 1258, 077
105	CH_3CH_2O-		O	base	B	87-900	(300 Mhz) ($CDCl_3$) 1.36 (t, J= 7.0 Hz, 3H), 3.68 (m, 2H), 3.78-3.99 (a.c., 6H), 4.33 (q, J= 7.0 Hz, 2H), 6.00 (d, J= 5.6 Hz, 1H), 7.69 (d, J= 7.9 Hz, 1H), 7.82 (dt, J= 7.9 Hz, J= 1.5 Hz, 1H), 8.05 (d, J= 5.6 Hz, 1H), 8.60 (d, J= 4.8 Hz, 1H).	(KBr) 1634, 1578, 1557, 1447, 1237, 1000

Sleep-inducing activity in mice

[0042] The sleep-inducing activity of the products of the present invention have been studied, evaluating the their capacity to increase the sleep time induced by barbital, according to a modification of the method described by David Sudgen (*J. Pharmacol. Exp. Ther.*, **1983**, 227, 3).

[0043] Fifteen minutes after the administration of barbital (150 mg/Kg, i.v.), the mice were treated with the product of the study at an initial dose of 100 mg/Kg (i.p.). For the most active products a dosage efficacy 50 (DE_{50}) was determined. The results for some of the products of the invention are shown in Table 2, taking meprobamate as the reference product.

Table 2

Capacity to increase the sleep time induced by barbital		
Example	% Activity (sleep) Dosage 100 mg/kg	DE_{50} (mg/kg)
2	93	14.4
4	100	8.7
8	97	9.7
9	67	28.1
10	74	11.6
11	89	10.5
13	77	41.3
15	86	8.2
17	56	84.2
18	82	27.3
22	57	75
24	69	41.5
26	60	74.1
30	75	37.2
32	73	56.5
34	98	7
55	70	31
57	100	1.6
59	101	14
61	102	4.5
63	103	4
65	100	7.7
67	96	15
69	97	10
73	98	9.5
81	99	8.3
83	100	5.3
87	101	10
89	102	8
91	81	10
92	98	8
94	84	5.2
96	97	3
Meprobamate	54	84.5

General anaesthetic activity

[0044] The general anaesthetic activity was study in mice, injecting the product of the study in the caudal vein. The start and duration time of sleep were recorded. The results for some of the products of the patent are shown in Table 3 and it can be seen that they show a clear anaesthetic activity with respect to the reference compound (Propofol),

with the animals recovering later.

Table 3.

Anaesthetic activity in mice, I.V. administration.			
Example	Dosage (mg/kg)	Start (s)	Duration (min)
2	80	Immediate	5.3
	40	12	0.6
4	80	Immediate	7.4
	40	15	1.3
15	80	20	1.9
	40	15	1.4
30	80	30	7.9
	40	30	1.8
34	80	Immediate	1.5
	40	No	0
57	80	Immediate	11
59	80	20	3.4
61	80	10	1.6
65	80	20	8.6
63	80	Immediate	14.8
71	80	60	5.6
73	80	Immediate	9
77	80	Immediate	10
79	80	Immediate	19
81	80	Immediate	10
85	80	Immediate	8.4
87	80	Immediate	10
89	80	Immediate	4
91	80	Immediate	7
92	80	Immediate	5
96	80	Immediate	6
101	80	Immediate	2
Propofol	106	30	6.2
	120	20	3.9
	80	No	0

Sedative activity

[0045] The sedative activity of some of the products on the locomotive activity of mice at different dosages has been studied. The technique described by T.G. Heffneren *J. Pharm. Exp. Ther.*, **1989**, 251, 105-112 has been followed. The measurement of the locomotive activity is carried out by dividing the rats into groups of four and determining the movement of the animals in an automated fashion using a video installation and the SMART program (Letica S.A.) for image analysis. The measurement of activity started 5 minutes after the administration of the product via i.p. and continued

for twenty minutes. The results (Figure 1) show the sedative effect of the compounds tested.

Muscular relaxant activity

[0046] The muscular relaxant activity has been studied in the products of the invention by evaluated their effect on the abdominal body tone of mice. following the method described by S. IRWING (Gordon Res. Conf. On Medicinal Chem., 1959, p. 133).

[0047] The mice received the products under study at a dosage of 80 mg/kg, via I.p., and at different times after administration (1/2, 1, 2, 3, 4 and 5 hours) the body tone and the abdominal tone was evaluated looking at the muscular tension compared to the control animals.

[0048] The results listed in Table 4 show that many of the products are noticeably active as muscular relaxants. This effect lasts longer than for propofol or zolpidem, which were used as reference products.

Table 4.

Miorelaxant activity in the Irwing mouse test. [Dosage = 80 mg/kg, i.p.]						
Example	% muscular relaxation at a time of:					
	1/2 H	1 H	2 H	3 H	4 H	5 H
4	100	90	10	0	0	0
34	60	70	80	85	40	40
57	100	100	100	80	55	0
63	100	100	90	75	20	0
71	100	100	100	40	10	0
73	100	100	100	0	0	0
75	100	100	100	80	80	60
77	100	100	100	60	0	0
79	100	100	100	65	0	0
83	90	90	90	70	50	0
92	100	100	100	0	0	0
propofol	100	100	70	0	0	0

Analgesic activity

[0049] The analgesic activity of the products of the invention have been studied by evaluation of their effect in the test of contortions induced by phenylbenzoquinone in mice, following the method described by Siegmund E., and coworkers (Proc. Soc. Exp. Biol. Med. 1957, 95: 729-731).

[0050] The mice received the products of the study, a different dosage levels, and one hour later they received an injections i.p. of 5 mg/kg of phenylbenzoquinone. The contortions of the mice were registered for the following fifteen minutes and compared with the contortions of the control group. The DE_{50} (dosage efficacy 50) of the compound of Example 4 is shown. This compound showed a better analgesic activity than aspirin, both when administered subcutaneously and orally.

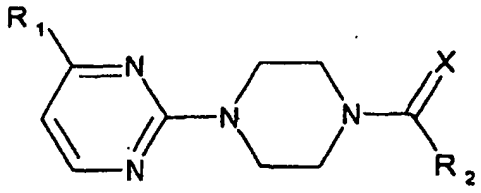
Table 5.

Analgesic activity. Protection from contortions induced by phenylbenzoquinone in mice.		
Example	DE_{50} (mg/kg, s.c.)	DE_{50} (mg/kg, o.a.)
Aspirin	84	120
4	48	72

Pharmaceutical formulations	
1. For injections (im/iv):	
Compound of Example 4	5 mg
Sodium chloride	c.s.
HCl 0.1 Nor NaOH	c.s.
Water for injection c.s.p.	3 ml
2. Capsules	
Compound of Example 4	0.5 to 4.0 mg
Colloidal silicon dioxide	0.5 mg
Magnesium stearate	1.0 mg
Lactose c.s.p.	100 mg
3. Tablets	
Compound of Example 4	0.5 to 4.0 mg
Colloidal silicon dioxide	0.5 mg
Magnesium stearate	1.0 mg
Sodium croscarmelose	60 mg
Lactose c.s.p.	100 mg
Formula B (humid granulation)	
Compound of Example 4	0.5 to 4.0 mg
Colloidal silicon dioxide	0.5 mg
Magnesium stearate	1.0 mg
Povidone K-30	5.0 mg
Sodium carboxymethylstarch	5.0 mg
Microcrystalline cellulose	20 mg
Lactose c.s.p.	100 mg

Claims

1. A derivative of acyl-piperazinyl-pyrimidine of general formula (I)



(I)

where

X is an oxygen or sulphur atom;

R_1 is a C_{1-4} alkoxy or trifluoromethyl radical;

R_2 is a C_{1-6} alkyl radical; C_{3-6} saturated cycloalkyl; heterocycloalkyl consisting of a ring of 3 to 6 atoms in which the heteroatom is selected from an atom of oxygen, sulphur or nitrogen, optionally N-substituted; phenyl optionally substituted with 1, 2 or 3 identical or different substituents selectred from fluorine, chlorine, bromine, amino, acetamido, nitro, methyl, trifluoromethyl and methoxy; arylalkyl consisting of a C_{1-3} alkyl group substituted by a phenyl radical optionally substituted by 1, 2 or 3 identical or different substituents selected from fluorine,

chlorine, bromo, amino, acetamido, nitro, methyl, trifluoromethyl and methoxy; heteroaryl consisting of a 5 or 6 heteroatom ring, optionally substituted, or of fused heteroaromatic systems optionally substituted, of 9 or 10 atoms consisting of 1 or 2 heteroatoms selected from oxygen, sulphur and nitrogen, selecting the aforementioned substituents from flourine, chlorine, bromine, amino, acetamido, nitro, methyl, trifluoromethyl and methoxy; and heteroarylalkyl consisting of an alkyl group of 1 to 3 carbon atmos substituted with a heteroaryl radical consisting of a 5 or 6 member heteroaromatic ring, optionally substituted, or of fused 9 to 10 member heteroaromatic systems, optionally substituted with 1 or 2 heteroatoms selected from oxygen, sulphur and nitrogen, selected the aforementioned substituents from fluorine, chlorine, bromine, amino, acetamido, nitro, methyl, trifluoromethyl and methoxy; and their physiologically acceptable salts.

2. A compound according to claim 1, in which R_1 is methoxy, ethoxy, propoxy, isopropoxy, butoxy, *sec*-butoxy or *tert*-butoxy.

3. A compound according to claim 1, in which R_2 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, isopentyl, neopentyl or hexyl.

4. A compound according to claim 1, in which R_2 is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

5. A compound according to claim 1, in which R_2 is 2-azyridinyl, 2-tetrahydrofuryl, 3-tetrahydrofuryl, 2-tetrahydrothienyl, 3-tetrahydrothienyl, 2-azetidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-piperidinyl, 3-piperidinyl or 4-piperidinyl.

6. A compound according to claim 1, in which R_2 is 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-clorophenyl, 3-clorophenyl, 4-clorophenyl, 2-bromophenyl, 3-bromophenyl, 4-bromophenyl, 2-aminophenyl, 3-aminophenyl, 4-aminophenyl, 2-nitrophenyl, 3-nitrophenyl, 4-nitrophenyl, 2-acetamidophenyl, 3-acetamidophenyl, 4-acetamidophenyl, 2-nitrophenyl, 3-nitrophenyl, 4-nitrophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-(trifluoromethyl)phenyl, 3-(trifluoromethyl)phenyl, 4-(trifluoromethyl)phenyl, 2-metoxyphenyl, 3-metoxyphenyl, 4-metoxyphenyl, 2,3-difluorophenyl, 3,4-difluorophenyl, 2,4-difluorophenyl, 2,3-dibromophenyl, 3,4-dibromophenyl, 2,4-dibromophenyl, 2,3-dimethylphenyl, 3,4-dimethylphenyl, 2,4-dimethylphenyl, 2,3-dimethoxyphenyl, 3,4-dimethoxyphenyl, 2,4-dimethoxyphenyl.

7. A compound according to claim 1, in which R_2 is phenylmethyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, optionally substituted at the aromatic ring.

8. A compound according to claim 1, in which R_2 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 3-methyl-2-thienyl, 5-methyl-2-thienyl, 3-methoxy-2-thienyl, 3-chloro-2-thienyl, 5-chloro-2-thienyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-indolyl, 3-indolyl, 2-benzo[b]thienyl, 3-benzyo[b]thienyl, 3-chloro-2-benzo[b]thienyl, pirazolyl, imidazolyl, pyrimidinyl, piridazinyl, pirazinyl, benzimidazolyl, quinolyl, oxazolyl or thiazolyl

9. A compound according to claim 1, in which R_2 is 2-thienylmethyl, 2-benzo[b]thienmethyl or 3-(4-chloropirazolyl) propyl.

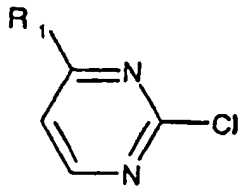
10. A compound according to claim 1, selected from the following group:

- 2-[4-(2-furylcarbonyl)-1-piperazinyl]-4-methoxypirimidine,
- 2-[4-(2-furylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine chlorohydrate,
- 4-methoxy-2-[4-(2-thienylcarbonyl)-1-piperazinyl]pyrimidine,
- 4-methoxy-2-[4-(2-thienylcarbonyl)-1-piperazinyl]pyrimidine chlorohydrate,
- 2-(4-acetyl-1-piperazinyl)-4-methoxypyrimidine,
- 2-{4-[4-(4-chloropyrazolyl)butanoyl]-1-piperazinyl}-4-methoxypyrimidine,
- 2-{4-[4-(4-chloropyrazolyl)butanoyl]-1-piperazinyl}-4-methoxypyrimidine chlorohydrate,
- 2-(4-benzoyl-1-piperazinyl)-4-methoxypyrimidine,
- 2-(4-cyclopropylcarbonyl-1-piperazinyl)-4-methoxypyrimidine,
- 2-[4-(2-furylcarbonyl)-1-piperazinyl]-4-(trifluoromethyl)pyrimidine,
- 2-[4-(2-thienylcarbonyl)-1-piperazinyl]-4-(trifluoromethyl)pyrimidine,
- 4-methoxy-2-[4-(3-thienylcarbonyl)-1-piperazinyl]pyrimidine,
- 4-methoxy-2-[4-(3-thienylcarbonyl)-1-piperazinyl]pyrimidine chlorohydrate,
- 2-[4-(5-methyl-2-thienylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine,
- 2-[4-(5-methyl-2-thienylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine chlroohydrate,

- 4-methoxy-2-[4-(3-methoxy-2-thienylcarbonyl)-1-piperazinyl]pyrimidine,
- 4-methoxy-2-[4-(3-methoxy-2-thienylcarbonyl)-1-piperazinyl]pyrimidine chlorohydrate,
- 2-[4-(2-benzo[b]thienylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine,
- 2-[4-(2-benzo[b]thienylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine chlorohydrate,
- 2-[4-(2-indolylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine,
- 2-[4-(3-chloro-2-benzo[b]thienylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine,
- 2-[4-(3-chloro-2-benzo[b]thienylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine chlorohydrate,
- 4-methoxy-2-[4-(2-pyrrolylcarbonyl)-1-piperazinyl]pyrimidine,
- 4-methoxy-2-[4-(2-pyrrolylcarbonyl)-1-piperazinyl]pyrimidine chlorohydrate,
- 4-methoxy-2-[4-(2-thienylacetyl)-1-piperazinyl]pyrimidine,
- 4-methoxy-2-[4-(2-thienylacetyl)-1-piperazinyl]pyrimidine chlorohydrate,
- 2-[4-(3-methyl-2-thienylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine,
- 2-[4-(3-methyl-2-thienylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine clorohydrate,
- 2-[4-(3-chloro-2-thienylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine,
- 2-[4-(3-chloro-2-thienylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine chlorohydrate,
- 2-[4-(3-indolylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine,
- 2-[4-(3-benzo[b]thienylacetyl)-1-piperazinyl]-4-methoxypyrimidine,
- 2-[4-(5-chloro-2-thienylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine,
- 2-[4-(5-chloro-2-thienylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine chlorohydrate,
- 4-methoxy-2-[4-(4-chlorobenzoyl)-1-piperazinyl]-4-methoxypyrimidine,
- 4-methoxy-2-[4-(4-chlorobenzoyl)-1-piperazinyl]-4-methoxypyrimidine chlorohydrate,
- 2-[4-(4-fluorobenzoyl)-1-piperazinyl]-4-methoxypyrimidine,
- 2-[4-(4-fluorobenzoyl)-1-piperazinyl]-4-methoxypyrimidine chlorohydrate,
- 2-[4-(4-chlorobenzoyl)-1-piperazinyl]-4-methoxypyrimidine,
- 2-[4-(4-chlorobenzoyl)-1-piperazinyl]-4-methoxypyrimidine chlorohydrate,
- 4-methoxy-2-[4-(3-methoxybenzoyl)-1-piperazinyl]pyrimidine,
- 4-methoxy-2-[4-(3-methoxybenzoyl)-1-piperazinyl]pyrimidine chlorohydrate,
- 2-[4-(3-fluorobenzoyl)-1-piperazinyl]-4-methoxypyrimidine,
- 2-[4-(3-fluorobenzoyl)-1-piperazinyl]-4-methoxypyrimidine chlorohydrate,
- 2-[4-(3-chlorobenzoyl)-1-piperazinyl]-4-methoxypyrimidine,
- 2-[4-(3-chlorobenzoyl)-1-piperazinyl]-4-methoxypyrimidine chlorohydrate,
- 4-methoxy-2-[4-(2-methoxybenzoyl)-1-piperazinyl]pyrimidine,
- 4-methoxy-2-[4-(2-methoxybenzoyl)-1-piperazinyl]pyrimidine chlorohydrate,
- 2-[4-(2-(fluorobenzoyl)-1-piperazinyl]-4-methoxypyrimidine,
- 2-[4-(2-(fluorobenzoyl)-1-piperazinyl]-4-methoxypyrimidine chlorohydrate,
- 2-[4-(2-(chlorobenzoyl)-1-piperazinyl]-4-methoxypyrimidine,
- 2-[4-(2-(chlorobenzoyl)-1-piperazinyl]-4-methoxypyrimidine chlorohydrate,
- 4-methoxy-2-[4-(2-tetrahydrofurylcarbonyl)-1-piperazinyl]pyrimidine,
- 4-methoxy-2-(4-thiobenzoyl-1-piperazinyl)pyrimidine,
- 4-methoxy-2-[4-(2-tetrahydrofurylcarbonyl)-1-piperazinyl]pyrimidine chlorohydrate,
- 4-methoxy-2-(4-thiobenzoyl-1-piperazinyl)pyrimidine chlorohydrate,
- 2-(4-benzoyl-1-piperazinyl)-4-methoxypyrimidine,
- 4-methoxy-2-{4-[4-(trifluoromethyl)benzoyl]-1-piperazinyl}pyrimidine.
- 4-methoxy-2-{4-[4-(trifluoromethyl)benzoyl]-1-piperazinyl}pyrimidine chlorohydrate,
- 4-methoxy-2-{4-[3-(trifluoromethyl)benzoyl]-1-piperazinyl}pyrimidine,
- 4-methoxy-2-{4-[3-(trifluoromethyl)benzoyl]-1-piperazinyl}pyrimidine chlorohydrate,
- 4-methoxy-2-{4-[2-(trifluoromethyl)benzoyl]-1-piperazinyl}pyrimidine,
- 4-methoxy-2-{4-[2-(trifluoromethyl)benzoyl]-1-piperazinyl}pyrimidine chlorohydrate,
- 4-methoxy-2-(4-nicotinoyl-1-piperazinyl)pyrimidine,
- 4-methoxy-2-(4-nicotinoyl-1-piperazinyl)pyrimidine dichlorohydrate,
- 2-(4-isonicotinoyl-1-piperazinyl)-4-methoxypyrimidine,
- 2-(4-isonicotinoyl-1-piperazinyl)-4-methoxypyrimidine dichlorohydrate,
- 2-[4-(1-imidazolylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine,
- 2-[4-(1-imidazolylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine chlorohydrate,
- 2-(4-nicotinoyl-1-piperazinyl)-4-(trifluoromethyl)pyrimidine,
- 2-(4-nicotinoyl-1-piperazinyl)-4-(trifluoromethyl)pyrimidine chlorohydrate,
- 4-methoxy-2-'4-(2-pyridylcarbonyl)-1-piperazinyl]pyrimidine,
- 4-methoxy-2-'4-(2-pyridylcarbonyl)-1-piperazinyl]pyrimidine dichlorohydrate,

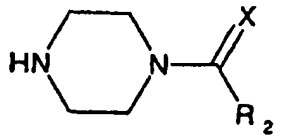
- 4-ethoxy-2-[4-(2-thienylcarbonyl)-1-piperazinyl]pyrimidine,
- 4-ethoxy-2-[4-(2-thienylcarbonyl)-1-piperazinyl]pyrimidine chlorohydrate,
- 2-[4-(3-chloro-2-thienylcarbonyl)-1-piperazinyl]-4-ethoxypyrimidine,
- 2-[4-(3-chloro-2-thienylcarbonyl)-1-piperazinyl]-4-ethoxypyrimidine chlorohydrate,
- 4-ethoxy-2-{4-[2-(trifluoromethyl)benzoyl]-1-piperazinyl}pyrimidine,
- 4-ethoxy-2-{4-[2-(trifluoromethyl)benzoyl]-1-piperazinyl}pyrimidine chlorohydrate,
- 2-[4-(2-methylbenzoyl)-1-piperazinyl]-4-methoxypyrimidine,
- 2-[4-(2-methylbenzoyl)-1-piperazinyl]-4-methoxypyrimidine chlorohydrate,
- 2-[4-(4-fluorobenzoyl)-1-piperazinyl]-4-isopropoxypyrimidine,
- 2-[4-(4-fluorobenzoyl)-1-piperazinyl]-4-isopropoxypyrimidine chlorohydrate,
- 4-isopropoxy-2-{4-[2-(trifluoromethyl)benzoyl]-1-piperazinyl]pyrimidine,
- 4-isopropoxy-2-{4-[2-(trifluoromethyl)benzoyl]-1-piperazinyl]pyrimidine chlorohydrate,
- 2-[4-(3-chloro-2-thiencarbonyl)-1-piperazinyl]-4-isopropoxypyrimidine,
- 2-[4-(3-chloro-2-thiencarbonyl)-1-piperazinyl]-4-isopropoxypyrimidine chlorohydrate
- 2-[4-(cyclohexylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine,
- 2-[4-(cyclohexylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine chlorohydrate,
- 4-ethoxy-2[4-(4-fluorobenzoyl]-1-piperazinyl}pyrimidine,
- 4-ethoxy-2[4-(4-fluorobenzoyl]-1-piperazinyl}pyrimidine chlorohydrate,
- 2-[4-(2-thiazolylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine,
- 2-[4-(2-aminobenzoyl)-1-piperazinyl]-4-methoxypyrimidine,
- 2-[4-(2-aminobenzoyl)-1-piperazinyl]-4-methoxypyrimidine chlorohydrate,
- 2-[4-(3-fluoro-2-thieylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine,
- 2-[4-(3-fluoro-3-thieylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine chlorohydrate,
- 2-[4-(4-methoxy-2-pyrimidinyl)-1-piperazinylcarbonyl]benzoic acid,
- 2-[4-(2-acetoxybenzoyl)-1-piperazinyl]-4-methoxypyrimidine,
- 2-[4-(2-hydroxybenzoyl)-1-piperazinyl]-4-methoxypyrimidine,
- sodium 2-[4-(4-methoxy-2-pyrimidinyl)-1-piperazinylcarbonyl]benzoate,
- 2-[4-(2-hydroxybenzoyl)-1-piperazinyl]-4-methoxypyrimidine hydrochlorate.
- 4-methoxy-2-[4-(2-methoxybenzoyl)-1-piperazinyl]-4-methoxypyrimidine, and
- 4-ethoxy-2[4-(2-pyridylcarbonyl]-1-piperazinyl]pyrimidine.

11. Procedure for the preparation of a compound of general formula (I), in which X represents an atom of oxygen, according to claim 1, which comprises reacting a derivative of the chloropyrimidine of formula (III)



(III)

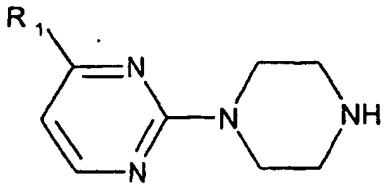
where R_1 has the meaning defined in claim 1,
with a derivative of piperazine of general formula (IV)



(IV)

where R_2 has the meaning defined in claim 1 and X represents an oxygen atom.

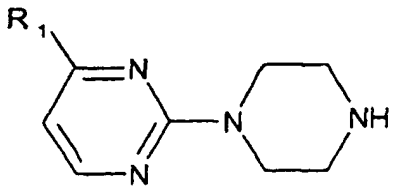
12. Procedure for the preparation of a compound of general formula (I) in which X represents an atom of oxygen, according to claim 1, which comprises reacting an amine of formula (V)



(V)

where R_1 has the meaning defined in claim 1,
with a carboxylic acid of formula R_2COOH (VI) or with a salt of said acid, in which R_2 has the meaning defined in claim 1.

13. Procedure for the preparation of a compound of general formula (I) in which X represents an oxygen atom, according to claim 1, which comprises reacting an amine of fonnula (V)



(V)

where R_1 has the meaning defined in claim 1
with a derivative reagent R_2COY (VII), in which R_2 has the meaning defined in claim 1 and Y represents a halogen atom, an azide group, a 1-imidazolyl group, a O-CO-R_4 group, where R_4 represents an alkyl radical of 1 to 6 atoms of carbon or an aryl radical, optionally substituted with one or several halogen atoms, or an OR_5 group where R_5 represents an aromatic group or one or two rings substituted with one or several halogen atoms or nitro radicals, or N-succinimide.

14. Procedure for the preparation of a compound of general formula (I) in which X represents a sulphur atom, according to claim 1, which comprises reacting a compound of general formula (I) in which X represents an oxygen atom, with Lawesson's reagent, (2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphaethano-2,4-disulphuride), or with phosphorous pentasulphide.

15. Procedure for the preparation of the physiologically acceptable salts of the compounds of general formula (I),

according to claim 1, which comprises reacting a compound of general formula (I) with a mineral acid or an organic acid in an appropriate solvent.

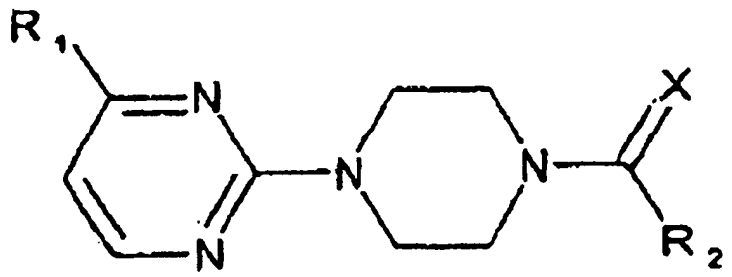
16. A pharmaceutical composition **characterised in that** it contains, in addition to a pharmaceutically acceptable excipient, at least one compound of general formula (I) or one of its physiologically acceptable salts, according to claims 1 to 10.

17. Use of a compound of general formula (I) or their pharmaceutically acceptable salts, according to any one of the claims 1 to 10, in the fabrication of a medicament with activity in the central nervous system of mammals, including man.

18. Use of a compound of general formula (I) or their pharmaceutically acceptable salts, according to any one of the claims 1 to 10, in the fabrication of a medicament with sedative, anticonvulsants. analgesic, muscular relaxant, antitusigenic, ansiolytic, antipsicotic, antidepressant, anti-cerebral ischeamic, anti-migraine activity, in the fabrication of a medicament for treating sleep disorders, neurodegenerative diseases. cognitive disorders and Alzheimer's disease, sleep-inducing or general anaesthetic agents, for mammals, including man.

Patentansprüche

1. Ein Azyl-piperazinyl-pyrimidinderivat der allgemeinen Formel (I)



(I)

wobei

X ein Sauerstoff- oder Schwefelatom ist;

R_1 ein C_{1-4} Alkoxy oder Trifluoromethylradikal ist;

R_2 ein C_{1-6} Alkylradikal ist; gesättigtes C_{3-6} Cykloalkyl; Heterocykloalkyl, das aus einem Ring von 3 bis 6 Atomen besteht, wobei das Heteroatom aus einem Atom von Sauerstoff, Schwefel, Stickstoff, der wahlweise N-substituiert ist; Phenyl, das wahlweise mit 1, 2 oder 3 identischen oder unterschiedlichen Substituenten substituiert wird, die zwischen Fluor, Chlor, Brom, Amino, Azetamido, Nitro, Methyl, Trifluormethyl und Methoxy gewählt werden; Arylalkyl, das aus einer C_{1-3} Alkylgruppe besteht, die durch ein Phenylradikal substituiert wird, das wahlweise durch 1, 2 oder 3 identische oder unterschiedliche Substituenten substitiert wird, die aus der Gruppe von Fluor, Chlor, Brom. Amin, Azetamido, Nitro, Methyl, Trifluomethyl und Methoxy gewählt werden; Heteroaryl, das aus einem Ring mit 5 oder 6 wahlweise substituierten Heteroatomen besteht oder wahlweise substituierten fusionierten Heteroatomsystemen, 9 oder 10 Atome, die aus 1 oder 2 Heteroatomen bestehen die zwischen Sauerstoff, Schwefel und Stickstoff gewählt werden, wobei die vorgenannten Substituenten zwischen Fluor, Chlor, Brom, Amino, Azetamido, Nitro, Methyl, Trifluormethyl und Methoxy gewählt werden; und Heteroarylalkyl, das aus einer Alkylgruppe von 1 bis 3 Kohnelstoffatomen besteht, die mit einem Heterorarylradikal substituiert werden, das aus einem 5 oder 6-gliedrigen heteroaromatischen Ring besteht, der wahlweise substituiert ist oder aus 9 bis 10-gliedrigen fusionierten heteroaromatischen Systemen, die wahlweise mit 1 oder 2 Heteroatomen substituiert werden, die zwischen Fluor, Chlor, Brom, Amino, Azetamido, Nitro, Methyl, Trifluormethyl und Methoxy gewählt werden und ihren physiologisch verträglichen Salzen gewählt wird.

2. Eine Verbindung gemäss Anspruch 1, in der R_1 Methoxy, Ethoxy, Propoxy, Isopropoxy, Butoxy, *sec*-Butoxy oder *tert*-Butoxy ist.

3. Eine Verbindung gemäss Anspruch 1, in der R_2 Methyl, Ethyl, Propyl, Isopropyl, Butyl, Isobutyl, *sec*-Butyl, *tert*-Butyl, Pentyl, Isopentyl, Neopentyl oder Hexyl ist.

4. Eine Verbindung gemäss Anspruch 1, in der R_2 Cyklopropyl, Cyklobutyl, Cyklopentyl oder Cyklohexyl ist.

5. Eine Verbindung gemäss Anspruch 1, in der R_2 2-Azyridinyl, 2-Tetrahydrofuryl, 3-Tetrahydrofuryl, 2-Tetrahydrothienyl, 3-Tetrahydrothienyl, 2-Azetidinyl, 2-Pyrrolidinyl, 3-Pyrrolidinyl, 2-Piperidinyl, 3-Piperidinyl oder 4-Piperidinyl ist.

6. Eine Verbindung gemäss Anspruch 1, in der R_2 2-Fluorphenyl, 3-Fluorphenyl, 4-Fluorphenyl, 2-Chlorphenyl, 3-Chlorphenyl, 4-Chlorphenyl, 2-Bromphenyl, 3-Bromphenyl, 4-Bromphenyl, 2-Aminophenyl, 3-Aminophenyl, 4-Aminophenyl, 2-Nitrophenyl, 3-Nitrophenyl, 4-Nitrophenyl, 2-Azetamidophenyl, 3-Azetamidophenyl, 4-Azetamidophenyl, 2-Nitrophenyl, 3-Nitrophenyl, 4-Nitrophenyl, 2-Methylphenyl, 3-Methylphenyl, 4-Methylphenyl, 2 (Trifluormethyl)phenyl, 3-(Trifluormethyl)phenyl, 4-(Trifluormethyl)phenyl, 2-Metoxyphenyl, 3-Metoxyphenyl, 4-Metoxyphenyl, 2,3-Difluorphenyl, 3,4-Difluorphenyl, 2,4-Difluorphenyl, 2,3-Dibromphenyl, 3,4-Dibromphenyl, 2,4-Dibromphenyl, 2,3-Dimethylphenyl, 3,4-Dimethylphenyl, 2,4-Dimethylphenyl, 2.3-Dimethoxyphenyl, 3,4-Dimethoxyphenyl, 2,4-Dimethoxyphenyl ist.

7. Eine Verbindung gemäss Anspruch 1, in der R_2 Phenylmethyl, 1-Phenylethyl, 2-Phenylethyl, 3-Phenylpropyl, wahlweise am aromatischen Ring substituiert, ist.

8. Eine Verbindung gemäss Anspruch 1, in der R_2 2-Furyl, 3-Furyl, 2-Thienyl, 3-Thienyl, 3-Methyl-2-thienyl, 5-Methyl-2-thienyl, 3-Methoxy-2-thienyl, 3-Chlor-2-thienyl, 5-Chlor-2-thienyl, 2-Pyrrolyl, 3-Pyrroryl, 2-Pyridyl, 3-Pyridyl, 4-Pyridyl, 2-Indolyl, 3-Indolyl, 2-Benzo[b]thienyl, 3-Benzo[b]thienyl, 3-Chlor-2-benzo[b]thienyl, Pirazolyl, Imidazolyl, Pyrimidinyl, Piridazinyl, Pirazinyl, Benzimidazolyl, Quinolyl, Oxazolyl oder Thiazolyl ist.

9. Eine Verbindung gemäss Anspruch 1, in der R_2 2-Thienylmethyl, 2-Benzo[b]thienmethyl oder 3-(4-Chlorpirazolyl) propyl ist.

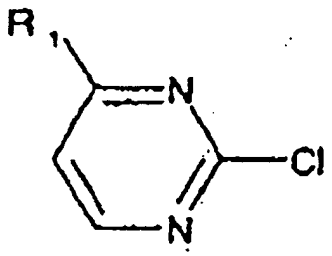
10. Eine Verbindung gemäss Anspruch 1, die von der folgenden Gruppe gewählt wird:

- 2-[4-(2-Furylcarbonyl)-1-piperazinyl]-4-methoxypyrimidin,
- 2-[4-(2-Furylcarbonyl)-1-piperazinyl]-4-methoxypyrimidinchlorhydrat,
- 4-Methoxy-2[4-(2-thienylcarbonyl)-1-piperazinyl]pyrimidin,
- 4-Methoxy-2[4-(2-thienylcarbonyl)-1-piperazinyl]pyrimidinchlorhydrat,
- 2-(4-Azetyl-1-piperazinyl)-4-methoxypyrimidin,
- 2-{4-[4(4-Chlorpyrazolyl)butanoyl]-1-piperazinyl}-4-methoxypyrimidin,
- 2-{4-[4(4-Chlorpyrazolyl)butanoyl]-1-piperazinyl}-4-methoxypyrimidinchlorhydrat,
- 2-(4-Benzoyl-1-piperazinyl)-4-methoxypyrimidin,
- 2-(4-Cyklopropylcarbonyl-1-piperazinyl)-4-methoxypyrimidin,
- 2-[4-(2-Furylcarbonyl)-1-piperazinyl]-4-(trifluourmethyl)pyrimidin,
- 2-[4-(2-Thienylcarbonyl)-1-piperazinyl]-4-(trifluourmethyl)pyrimidin,
- 4-Methoxy-2[4-(3-thienylcarbonyl)-1-piperazinyl]pyrimidin,
- 4-Methoxy-2[4-(3-thienylcarbonyl)-1-piperazinyl]pyrimidinchlorhydrat,
- 2-[4-(5-Methyl-2-thienylcarbonyl)-1-piperazinyl]-4-methoxypyrimidin,
- 2-[4-(5-Methyl-2-thienylcarbonyl)-1-piperazinyl]-4-methoxypyrimidinchlorhydrat,
- 4-Methoxy-2[4-(3-methoxy-2-thienylcarbonyl)-1-piperazinyl]pyrimidin,
- 4-Methoxy-2[4-(3-methoxy-2-thienylcarbonyl)-1-piperazinyl]pyrimidinchlorhydrat,
- 2-[4-(2-Benzo[b]thienylcarbonyl)-1-piperazinyl]-4-methoxypyrimidin,
- 2-[4-(2-Benzo[b]thienylcarbonyl)-1-piperazinyl]-4-methoxypyrimidinchlorhydrat,
- 2-[4-(2-Indolylcarbonyl)-1-piperazinyl]-4-methoxypyrimidin,
- 2-[4-(3-Chlor-2-benzo[b]thienylcarbonyl)-1-piperazinyl]-4-methoxypyrimidin,
- 2-[4-(3-Chlor-2-benzo[b]thienylcarbonyl)-1-piperazinyl]-4-methoxypyrimidinchlorhydrat,
- 4-Methoxy-2[4-(2-pyrrolylcarbonyl)-1-piperazinyl]pyrimidin,
- 4-Methoxy-2[4-(2-pyrrolylcarbonyl)-1-piperazinyl]pyrimidinchlorhydrat,

- 4-Methoxy-2[4-(2-thienylazetyl)-1-piperazinyl]pyrimidin,
- 4-Methoxy-2[4-(2-thienylazetyl)-1-piperazinyl]pyrimidinchlorhydrat,
- 2-[4-(3-Methyl-2-thienylcarbonyl)-1-piperazinyl]-4-methoxypyrimidin,
- 2-[4-(3-Methyl-2-thienylcarbonyl)-1-piperazinyl]-4-methoxypyrimidinchlorhydrat,
- 2-[4-(3-Chlor-2-thienylcarbonyl)-1-piperazinyl]-4-methoxypyrimidin,
- 2-[4-(3-Chlor-2-thienylcarbonyl)-1-piperazinyl]-4-methoxypyrimidinchlorhydrat,
- . 2-[4-(3-Indolylcarbonyl)-1-piperazinyl]-4-methoxypyrimidin,
- 2-[4-(3-Benzo[b]thienylazetyl)-1-piperazinyl]-4-methoxypyrimidin,
- 2-[4-(5-Chloro-2-thienylcarbonyl)-1-piperazinyl]-4-methoxypyrimidin,
- 2-[4-(5-Chloro-2-thienylcarbonyl)-1-piperazinyl]-4-methoxypyrimidinchlorhydrat,
- 4-Methoxy-2[4-(4-chlorbenzoyl)-1-piperazinyl]methoxypyrimidin,
- 4-Methoxy-2[4-(4-chlorbenzoyl)-1-piperazinyl]methoxypyrimidinchlorhydrat,
- 2-[4-(4-Fluorbenzyl)-1-piperazinyl]-4-methoxypyrimidin,
- 2-[4-(4-Fluorbenzyl)-1-piperazinyl]-4-methoxypyrimidinchlorhydrat,
- 2-[4-(4-Chlorbenzyl)-1-piperazinyl]-4-methoxypyrimidin,
- 2-[4-(4-Chlorbenzyl)-1-piperazinyl]-4-methoxypyrimidinchlorhydrat
- 4-Methoxy-2[4-(3-methoxybenzoyl)-1-piperazinyl]pyrimidin,
- 4-Methoxy-2[4-(3-methoxybenzoyl)-1-piperazinyl]pyrimidinchlorhydrat,
- 2-[4-(3-Fluorbenzyl)-1-piperazinyl]-4-methoxypyrimidin,
- 2-[4-(3-Fluorbenzyl)-1-piperazinyl]-4-methoxypyrimidinchlorhydrat,
- 2-[4-(3-Chlorbenzyl)-1-piperazinyl]-4-methoxypyrimidin,
- 2-[4-(3-Chlorbenzyl)-1-piperazinyl]-4-methoxypyrimidinchlorhydrat
- 4-Methoxy-2[4-(2-methoxybenzoyl)-1-piperazinyl]pyrimidin,
- 4-Methoxy-2[4-(2-methoxybenzoyl)-1-piperazinyl]pyrimidinchlorhydrat,
- 2-[4-(2-Fluorbenzyl)-1-piperazinyl]-4-methoxypyrimidin,
- 2-[4-(2-Fluorbenzyl)-1-piperazinyl]-4-methoxypyrimidinchlorhydrat,
- 2-[4-(2-Chlorbenzyl)-1-piperazinyl]-4-methoxypyrimidin,
- 2-[4-(2-Chlorbenzyl)-1-piperazinyl]-4-methoxypyrimidinchlorhydrat
- 4-Methoxy-2[4-(2-tetrahydrofurylcarbonyl)-1-piperazinyl]pyrimidin,
- 4-Methoxy-2(4-tiobenzoyl-1-piperazinyl)pyrimidin,
- 4-Methoxy-2[4-(2-tetrahydrofurylcarbonyl)-1-piperazinyl]pyrimidinchlorhydrat,
- 4-Methoxy-2(4-tiobenzoyl-1-piperazinyl)pyrimidinchlorhydrat,
- 2-(4-Benzoyl-1-piperazinyl)-4-methoxypyrimidin,
- 4-Methoxy-2{4-[4-(trifluormethyl)benzoyl]-1-piperazinyl}pyrimidin,
- 4-Methoxy-2{4-[4-(trifluormethyl)benzoyl]-1-piperazinyl}pyrimidinchlorhydrat,
- 4-Methoxy-2{4-[3-(trifluormethyl)benzoyl]-1-piperazinyl}pyrimidin,
- 4-Methoxy-2{4-[3-(trifluormethyl)benzoyl]-1-piperazinyl}pyrimidinchlorhydrat,
- 4-Methoxy-2{4-[2-(trifluormethyl)benzoyl]-1-piperazinyl}pyrimidin,
- 4-Methoxy-2{4-[2-(trifluormethyl)benzoyl]-1-piperazinyl}pyrimidinchlorhydrat,
- 4-Methoxy-2(4-nikotinoyl-1-piperazinyl)pyrimidin,
- 4-Methoxy-2(4-nikotinoyl-1-piperazinyl)pyrimidinchlorhydrat,
- 2-(4-Isonikotinoyl-1-piperazinyl)-4-methoxypyrimidin,
- 2-(4-Isonikotinoyl-1-piperazinyl)-4-methoxypyrimidinchlorhydrat,
- 2-[4-(1-Imidazolylcarbonyl)-1-piperazinyl]-4-methoxypyrimidin,
- 2-[4-(1-Imidazolylcarbonyl)-1-piperazinyl]-4-methoxypyrimidinchlorhydrat,
- 2-(4-Nikotinoyl-1-piperazinyl)-4-(trifluormethyl)pyrimidin,
- 2-(4-Nikotinoyl-1-piperazinyl)-4-(trifluormethyl)pyrimidinchlorhydrat,
- 4-Methoxy-2-'4-(2-pyridylcarbonyl)-1-piperazinylpyrimidin,
- 4-Methoxy-2-'4-(2-pyridylcarbonyl)-1-piperazinylpyrimidindichlorhydrat,
- 4-Ethoxy-2[4-(2-thienylcarbonyl)-1-piperazinyl]pyrimidin,
- 4-Ethoxy-2[4-(2-thienylcarbonyl)-1-piperazinyl]pyrimidinchlorhydrat,
- 2-[4-(3-Chlor-2-thienylcarbonyl)-1-piperazinyl]-4-ethoxypyrimidin,
- 2-[4-(3-Chlor-2-thienylcarbonyl)-1-piperazinyl]-4-ethoxypyrimidinchlorhydrat,
- 4-Ethoxy-2{4[2-(trifluormethyl)benzoyl)-1-piperazinyl]pyrimidin,
- 4-Ethoxy-2{4[2-(trifluormethyl)benzoyl)-1-piperazinyl]pyrimidinchlorhydrat,
- 2-[4-(2-Methylbenzoyl)-1-piperazinyl]-4-methoxypyrimidin,
- 2-[4-(2-Methylbenzoyl)-1-piperazinyl]-4-methoxypyrimidinchlorhydrat,
- 2-[4-(4-Fluorbenzoyl)-1-piperazinyl]-4-isopropoxypyrimidin,

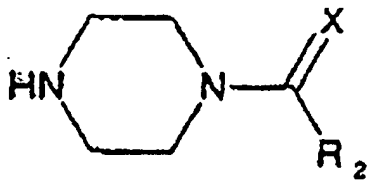
- 2-[4-(4-Fluorbenzoyl)-1-piperazinyl]-4-isopropoxypyrimidinchlorhydrat,
- 4-Isoproxy-2{4-[2-(trifluormethyl)benzoyl]-1-piperazinyl}pyrimidin,
- 4-Isoproxy-2 {4-[2-(trifluormethyl)benzoyl]-1-piperazinyl}pynmidinchtorhydrat
- 2-[4-(3-Chlor-2-thiencarbonyl)-1-piperazinyl]-4-isoproxypyrimidin,
- 2-[4-(3-Chlor-2-thiencarbonyl)-1-piperazinyl]-4-isoproxypyrimidin,
- 2-[4-(Cyklohexylcarbonyl)-1-piperazinyl]-4-methoxypyrimidin,
- 2-[4-(Cyklohexylcarbonyl)-1-piperazinyl]-4-methoxypyrimidinchlorhydrat,
- 4-Ethoxy-2[4-(4-fluorbenzoyl)-1-piperazinyl]pyrimidin,
- 4-Ethoxy-2[4-(4-fluorbenzoyl)-1-piperazinyl]pyrimidinchlorhydrat,
- 2-[4-(2-Thiazolylcarbonyl)-1-piperazinyl]-4-methoxypyrimidin,
- 2-[4-(2-Aminobenzoyl)-1-piperazinyl]-4-methoxypyrimidin,
- 2-[4-(2-Aminobenzoyl)-1-piperazinyl]-4-methoxypyrimidinchlorhydrat,
- 2-[4-(3-Fluor-2-Thielylcarbonyl)-1-piperazinyl]-4-methoxypyrimidin,
- 2-[4-(3-Fluor-2-Thielylcarbonyl)-1-piperazinyl]-4-methoxypyrimidinchlorhydrat,
- 2-[4-(4-Methoxy-2-pyrimidinil)-1-piperazinylcarbonyl]benzoesäure,
- 2-[4-(2-Azetoxybenzoyl)-1-piperazinyl]-4-methoxypyrimidin,
- 2-[4-(2-Hydroxybenzoyl)-1-piperazinyl]-4-methoxypyrimidin,
- Sodium 2-[4-(4-Methoxy-2-pyrimidinil)-1-piperazinylcarbonyl]benzoat
- 2-[4-(2-Hydroxybenzoyl)-1-piperazinyl]-4-methoxypyrimidinhydrochlorat,
- 4-Methoxy-2-[4-(2-methoxybenzoyl)-1-piperazinyl]-4-methoxypyrimidin und
- 4-Ethoxy-2-[4-(2-pyridylcarbonyl)-1-piperazinyl]pyrimidin

11. Verfahren zur Herstellung einer Verbindung der allgemeinen Formel (I), in der X ein Sauerstoffatom darstellt, gemäss Anspruch 1, das die Reaktion eines Derivats des Chlorpyrimidin der Formel (III) umfasst,



(III)

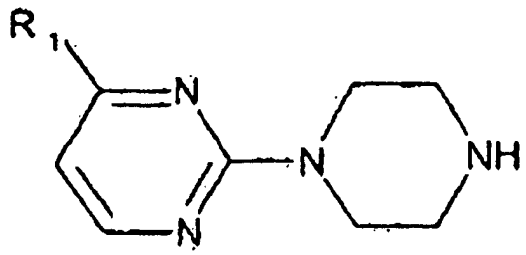
wobei R_1 die im Anspruch 1 definierte Bedeutung hat,
mit einem Piperazinderivat der allgemeinen Formel (IV),



(IV)

wobei R_2 die im Anspruch 1 definierte Bedeutung hat und X ein Sauerstoffatom darstellt.

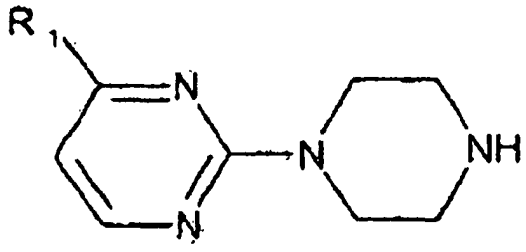
12. Verfahren zur Herstellung einer Verbindung der allgemeinen Formel (I), in der X ein Sauerstoffatom darstellt, gemäss Anspruch 1, das die Reaktion eines Amins der Formel (V) umfasst,



(V)

wobei R_1 die im Anspruch 1 definierte Bedeutung hat,
mit einer Carbonsäure der Formel R_2COOH (VI) oder einem Salz der besagten Säure,
wobei R_2 die im Anspruch 1 definierte Bedeutung hat.

13. Verfahren zur Herstellung einer Verbindung der allgemeinen Formel (I), in der X ein Sauerstoffatom darstellt, gemäss Anspruch 1, das die Reaktion eines Amins der Formel (V) umfasst,



(V)

wobei R_1 die im Anspruch 1 definierte Bedeutung hat,
mit einem einem derivativen Reagens R_2COY (VII), wobei R_2 die im Anspruch 1 definierte Bedeutung hat und Y ein Halogenatom, eine Azidgruppe, eine 1-Imidazolylgruppe, eine O-CO-R_4-Gruppe, wobei R_4 ein Alkylradikal mit 1 bis 6 Kohlenstoffatomen oder einem Arylradikal darstellt, das wahlweise durch eine oder mehrere Halogenatome substituiert wird oder ein OR_5, wobei R_5 eine aromatische Gruppe oder einen oder zwei Ringe darstellt, die durch ein oder mehrere Halogenatome oder Nitroradikale substituiert sind oder N-Succinimid darstellt.

14. Verfahren zur Herstellung einer Verbindung der allgemeinen Formel (I), in der X ein Schwefelatom darstellt, gemäss Anspruch 1, das die Reaktion einer Verbindung der Formel (I) umfasst, wobei X ein Sauerstoffatom darstellt mit einem Lawessonreagens, (2,4-bis(4-Methoxyphenyl)-1,3,2,4-dithiadiphosphaetan-2,4-disulfurid) oder mit Phosphorpentasulfid.

15. Verfahren zur Herstellung der physiologisch verträglichen Salz der Verbindungen der allgemeinen Formel (I) gemäss Anspruch 1, das die Reaktion einer Verbindung der allgemeinen Formel (I) mit einer Mineralsäure oder einer organischen Säure in einem geeigneten Lösemittel umfasst.

16. Eine farmazeutische Zusammensetzung, **dadurch gekennzeichnet, dass** sie zusätzlich zu einem farmazeutisch zulässigen Trägerstoff wenigstens eine Verbindung der allgemeinen Formel (I) oder eins der physiologisch verträglichen Salze enthält gemäss den Ansprüchen 1 bis 10.

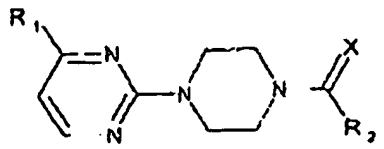
17. Verwendung einer Verbindung der allgemeinen Formel (I) oder ihrer farmazeutisch verträglichen Salze, gemäss einem der Ansprüche 1 bis 10 zur Herstellung eines Medikaments mit Aktivität im zentralen Nervensystem von Säugetieren, eingeschlossen Menschen.

18. Verwendung einer Verbindung der allgemeinen Formel (I) oder ihrer farmazeutisch verträglichen Salze, gemäss einem der Ansprüche 1 bis 10 zur Herstellung eines Medikaments mit sedativer, antikonvulsiver, analgetischer,

muskelentspannender, hustenlindemder, ansiolytischer, antipsychotischer, antidepressiver, antizerebralischämischer, antimigräne Aktivität bei der Herstellung eines Medikaments zur Behandlung von Schlafstörungen, neurodegenerativen Erkrankungen, kognitiven Erkrankungen und Alzheimer, für Schlafförderungs- oder allgemeine analgetische Wirkstoffe für Säugetiere, eingeschlossen Menschen.

Revendications

1. Un dérivé d'acyl-pipérazinyl-pyrimidine de formule générale (I)



(I)

dans laquelle

X est un atome e d'oxygène ou de soufre ;

R_1 est un radicales alcoxi C_{1-4} ou trifluorométhyle ;

R_2 est un radical alkyle C_{1-6}, cycloalkyle saturé C_{3-6} ; hétérolalkyle consistant en un anneau de 3 à 6 atomes dans lequel l'hétéroatome est choisi parmi un atome d'oxygène, soufre ou nitrogène, optionnellement N-substitué ; phényle optionnellement substitué avec 1, 2 ou 3 substituants identiques ou différents choisis parmi le fluor, le chlore, le brome, l'amino, l'acétamido, le nitro, le méthyle, le trifluorométhyle et le méthoxy ; l'arylalkyle consistant en un groupe alkyle C_{1-3} substitué par un radicale phényle optionnellement substitué par 1, 2 ou 3 substituants identiques ou différents choisis parmi le fluor, le chlore, le brome, l'amino, l'acétamido, le nitro, le méthyle, le trifluorométhyle et le méthoxy, l'hétéroaryle consistant en un anneau de 5 ou 6 hétéroatomes optionnellement substitué, ou en des systèmes hétéroaromatiques fondus optionnellement substitués, de 9 ou 10 atomes consistant en 1 ou 2 hétéroatomes choisis parmi l'oxygène, le soufre et le nitrogène, en choisissant les substituants précités parmi le fluor, le chlore, le brome, l'amino, l'acétamido, le nitro, le méthyle, le trifluorométhyle et le méthoxy ; et l'hétéroarylalkyle consistant en un groupe alkyle de 1 à 3 atomes de carbone substitués par un radical hétéroaryle consistant en un anneau hétéroaromatique de 5 à 6 membres, optionnellement substitués, ou en des systèmes hétéroaromatiques de 9 à 10 membres fondus, optionnellement substitués par 1 ou 2 hétéroatomes choisis parmi l'oxygène, le soufre et le nitrogène, les substituants précités étant choisis parmi le fluor, le chlore, le brome, l'amino, l'acétamido, le nitro, le méthyle, le trifluorométhyle et le méthoxy ; et leurs sels physiologiquement acceptables.

2. Un composé selon la revendication 1, dans lequel R_1 es méthoxy, éthoxy, propoxy, isopropoxy, butoxy, *sec*-butoxy ou *tert*-butoxy.

3. Un composé selon la revendication 1, dans lequel R_2 est méthyle, éthyle, propyle, isopropyle, butyle, isobutyle, *sec*-butyle, *tert*-butyle, pentyle, isopentyle, néopentyle ou hexyle.

4. Un composé selon la revendication 1, dans lequel R_2 est cyclopropyle, cyclobutyle, cyclopentyle ou cyclohexyle.

5. Un composé selon la revendication 1, dans lequel R_2 est 2-aziridinyle, 2-tétrahydrofuryle, 3-tétrahydrofuryle, 2-tétrahydrothiènyle, 3-tétrahydrothiènyle, 2-azétidinyle, 2-pyrrolidinyle, 3-pyrrolidinyle, 2-pipéridinyle, 3-pipéridinyle ou 4-pipéridinyle.

6. Un composé selon la revendication 1, dans lequel, R_2 est 2-fluorophényle, 3-fluorophényle, 4-fluorophényle, 2-chlorophényle, 3-chlorophényle, 4-chlorophényle, 2-bromophényle, 3-bromophényle, 4-bromophényle, 2-aminophényle, -aminophényle, 4-aminophényle, 2-nitrophényle, 3-nitrophényle, 4-nitrophényle, 2-acétamidophényle, 3-acétamidophényle, 4-acétamidophényle, 2-nitrophényle, 3-nitrophényle, 4-nitrophényle, 2-méthylphényle, 3-méthylphényle, 4-méthylphényle, 2-(trifluorométhyl)phényle, 3-(trifluorométhyl)phényle, 4-(trifluorométhyl)phényle, 2-méthoxyphényle, 3-méthoxyphényle, 4-méthoxyphényle, 2,3-difluorophényle, 3,4-difluorophényle, 2,4-difluorophényle, 2,3-dibromophényle, 3,4-dibromophényle, 2,4-dibromophényle, 2,3-diméthylphényle, 3,4-diméthylphényle, 2,4-diméthylphényle, 2,3-diméthoxyphényle, 3,4-diméthoxyphényle, 2,4-diméthoxyphényle.

7. Un composé selon la revendication 1, dans lequel R_2 est phénylméthyle, 1-phényléthyle, 2-phényléthyle, 3-phénylpropyle optionnellement substitué à l'anneau aromatique.

8. Un composé selon la revendication 1, dans lequel R_2 est 2-furyle, 3-furyle, 2-thiényle, 3-thiényle, 3-méthyl-2-thiényle, 5-méthyl-2-thiényle, 3-méthoxy-2-thiényle, 3-chloro-2-thiényle, 5-chloro-2-thiényle, 2-pyrrolyle, 3-pyrrolyle, 2-pyridyle, 3-pyridyle, 4-pyridyle, 2-indolyle, 3.indolyle, 2-benzo[b]thiényle, 3-benzo[b]thiényle, 3-clhoro-2-benzo [b]thiényle, pirazolyle, imidazolyle, pyrimidinyle, piridazinyle, pirazinyle, benzimidazolyle, quinolyle, oxazolyle ou thiazolyle.

9. Un composé selon la revendication 1, où R_2 est 2-thiènylméthyl, 2-benzo[b]thiènylmétyl ou 3-(4-chloropirazolyl) propyle.

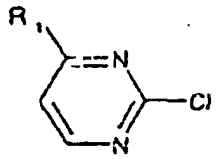
10. Un composé selon la revendication 1, choisi parmi le groupe suivant :

- 2-[4-(2-furylcarbonyl)-1-pipérazinyl]-4-méthoxypyrimidine,
- chlorhydrate de 2-[4-(2-furylcarbonyl)-1-pipérazinyl]-4-méthoxypyrimidine,
- 4-méthoxy-2-[4-(2-thiénylcarbonyl)-1-pipérazinyl]pyrimidine
- chlorhydrate de 4-méthoxy-2-[4-(2-thiénylcarbonyl)-1-pipérazinyl]pyrimidine,
- 2-(4-acétyl-1-pipérazinyl)-4-méthoxypyrimidine,
- 2-{4-[4-(4-chloropyrazolyl)butanoyl]-1-pipérazinyl}-4-méthoxypyrimidine
- chlorhydrate de 2-{4-[4-(4-chloropyrazolyl)butanoyl]-1-pipérazinyl}-4-méthoxypyrimidine
- 2-(4-benzoyl-1-pipérazinyl)-4-méthoxypyrimidine,
- 2-(4-cyclopropylcarbonyl-1-pipérazinyl]-4-méthoxypyrimidine,
- 2-[4-(2-furylcarbonyl)-1-pipérazinyl]-4-(trifluorométhyl)pyrimidine,
- 2-[4-(2-thiènylcarbonyl)-1-pipérazinyl]-4-(trifluorométhyl)pyrimidine
- 4-méthoxy-2-[4-(3-thiénylcarbonyl)-1-pipérazinyl]pyrimidine
- chlorhydrate de 4-méthoxy-2-[4-(2-thiénylcarbonyl)-1-pipérazinyl]pyrimidine,
- 2-[4-(5-méthyl-2-thiénylcarbonyl)-1-pipérazinyl]-4-méthoxypyrimidine,
- chlorhydrate de 2-[4-(5-méthyl-2-thiénylcarbonyl)-1-pipérazinyl]-4-méthoxypyrimidine,
- 4-méthoxy-2-[4-(3-méthoxy-2-thiénylcarbonyl)-1-pipérazinyl]pyrimidine
- chlorhydrate de 4-méthoxy-2-[4-(3-méthoxy-2-thiénylcarbonyl)-1-pipérazinyl]pyrimidine
- 2-[4-(2-benzo[b]thiénylcarbonyl)-1-pipérazinyl]-4-méthoxypyrimidine,
- chlorhydrate de 2-[4-(2-benzo[b]thiénylcarbonyl)-1-pipérazinyl]-4-méthoxypyrimidine
- 2-[4-(2-indolylcarbonyl)-1-pipérazinyl]-4-méthoxypyrimidine
- 2-[4-(3-chloro-2-benzo[b]thiénylcarbonyl)-1-pipérazinyl]-4-méthoxypyrimidine
- chlorhydrate de 2-[4-(3-chloro-2-benzo[b]thiénylcarbonyl)-1-pipérazinyl]-4-méthoxypyrimidine
- 4-méthoxy-2-[4-(2-pyrrolylcarbonyl)-1-pipérazinyl]pyrimidine
- chlorhydrate de 4-méthoxy-2-[4-(2-pyrrolylcarbonyl)-1-pipérazinyl]pyrimidine,
- 4-méthoxy-2-[4-(2-thiénylacétyle)-1-pipérazinyl]pyrimidine
- chlorhydrate de 4-méthoxy-2-[4-(2-thiénylacéthyl)-1-pipérazinyl]pyrimidine,
- 2-[4-(3-méthyl-2-thiénylcarbonyl)-1-pipérazinyl]-4-méthoxypyrimidine
- chlorhydrate de 2-[4-(3-méthyl-2-thiénylcarbonyl)-1-pipérazinyl]-4-méthoxypyrimidine
- 2-[4-(3-chloro-2-thiénylcarbonyl)-1-pipérazinyl]-4-méthoxypyrimidine
- chlorhydrate de 2-[4-(3-chloro-2-thiénylcarbonyl)-1-pipérazinyl]-4-méthoxypyrimidine,
- 2-[4-(3-indolylcarbonyl)-1-pipérazinyl]-4-méthoxypyrimidine
- 2-[4-(3-benzo[b]thiénylacétyl)-1-pipérazinyl]-4-méthoxypyrimidine
- 2-[4-(5-chloro-2-thiénylcarbonyl)-1-pipérazinyl]-4-méthoxypyrimidine
- chlorhydrate de 2-[4-(5-chloro-2-thiénylcarbonyl)-1-pipérazinyl]-4-méthoxypyrimidine
- 4-méthoxy-2-[4-(4-chlorobenzoyl)-1-pipérazinyl]-4-méthoxypyrimidine
- chlorhydrate de 4-méthoxy-2-[4-(4-chlorobenzoyl)-1-pipérazinyl]-4-méthoxypyrimidine
- 4-méthoxy-2-[4-(2-pyrrolylcarbonyl)-1-pipérazinyl]pyrimidine,
- 2-[4-(4-fluorobenzoyl)-1-pipérazinyl]-4-méthoxypyrimidine
- chlorhydrate de 2-[4-(4-fluorobenzoyl)-1-pipérazinyl]-4-méthoxypyrimidine,
- 2-[4-(4-chlorobenzoyl)-1-pipérazinyl]-4-méthoxypyrimidine
- chlorhydrate de 2-[4-(4-chlorobenzoyl)-1-pipérazinyl]-4-méthoxypyrimidine,
- 4-méthoxy-2-[4-(3-méthoxybenzoyl)-1-pipérazinyl]pyrimidine,
- chlorhydrate de 4-méthoxy-2-[4-(3-méthoxybenzoyl)-1-pipérazinyl]pyrimidine,
- 2-[4-(3-fluorobenzoyl)-1-pipérazinyl]-4-méthoxypyrimidine

- chlorhydrate de 2-[4-(3-fluorobenzoyl)-1-pipérazinyl]-4-méthoxypyrimidine
- 2-[4-(3-chlorobenzoyl)-1-pipérazinyl]-4-méthoxypyrimidine
- chlorhydrate de 2-[4-(3-chlorobenzoyl)-1-pipérazinyl]-4-méthoxypyrimidine
- 4-méthoxy-2-[4-(2-méthoxybenzoyl)-1-pipérazinyl]pyrimidine,
- chlorhydrate de 4-méthoxy-2-[4-(2-méthoxybenzoyl)-1-pipérazinyl]pyrimidine,
- 2-[4-(2-(fluorobenzoyl)-1-pipérazinyl]-4-méthoxypyrimidine
- chlorhydrate de 2-[4-(2-(fluorobenzoyl)-1-pipérazinyl]-4-méthoxypyrimidine
- 2-[4-(2-(chlorobenzoyl)-1-pipérazinyl]-4-méthoxypyrimidine
- chlorhydrate de 2-[4-(2-(chlorobenzoyl)-1-pipérazinyl]-4-méthoxypyrimidine
- 4-méthoxy-2-[4-(2-tétrahydrofurylcarbonyl)-1-pipérazinyl]pyrimidine,
- 4-méthoxy-2-(4-thiobenzoyl-1-pipérazinyl)pyrimidine,
- chlorhydrate de 4-méthoxy-2-[4-(2-tétrahydrofurylcarbonyl)-1-pipérazinyl]pyrimidine,
- chlorhydrate de 4-méthoxy-2-(4-thiobenzoyl-1-pipérazinyl)pyrimidine,
- 2-(4-benzoyl-1-pipérazinyl)-4-méthoxypyrimidine,
- 4-méthoxy-2-{4-[4-(trifluorométhyl)benzoyl]-1-pipérazinyl}pyrimidine,
- chlorhydrate de 4-méthoxy-2-{4-[4-(trifluorométhyl)benzoyl]-1-pipérazinyl}pyrimidine,
- 4-méthoxy-2-{4-[3-(trifluorométhyl)benzoyl]-1-pipérazinyl]pyrimidine,
- chlorhydrate de 4-méthoxy-2-{4-[3-(trifluorométhyl)benzoyl]-1-pipérazinyl}pyrimidine,
- 4-méthoxy-2-{4-[2-(trifluorométhyl)benzoyl]-1-pipérazinyl]pyrimidine,
- chlorhydrate de 4-méthoxy-2-{4-[2-(trifluorométhyl)benzoyl]-1-pipérazinyl}pyrimidine,
- 4-méthoxy-2-(4-nicotinoyl-1-pipérazinyl)pyrimidine,
- dichlorhydrate de 4-méthoxy-2-(4-nicotinoyl-1-pipérazinyl)pyrimidine,
- 2-(4-isonicotinoyl-1-pipérazinyl)-4-méthoxypyrimidine,
- dichlorhydrate de 2-(4-isonicotinoyl-1-pipérazinyl)-4-méthoxypyrimidine,
- 2-[4-(1-imidazolylcarbonyl)-1-pipérazinyl]-4-méthoxypyrimidine,
- chlorhydrate de 2-[4-(1-imidazolylcarbonyl)-1-pipérazinyl]-4-méthoxypyrimidine,
- 2-(4-nicotinoyl-1-pipérazinyl)-4-(trifluorométhyl)pyrimidine,
- chlorhydrate de 2-(4-nicotinoyl-1-pipérazinyl)-4-(trifluorométhyl)pyrimidine,
- 4-méthoxy-2-[4-(2-piridylcarbonyl)-1-pipérazinyl]pyrimidine,
- dichlorhydrate de 4-méthoxy-2-[4-(2-piridylcarbonyl)-1-pipérazinyl]pyrimidine,
- 4-éthoxy-2-[4-(2-thiénylcarbonyl)-1-pipérazinyl]pyrimidine,
- chlorhydrate de 4-éthoxy-2-[4-(2-thiénylcarbonyl)-1-pipérazinyl]pyrimidine,
- 2-[4-(3-chloro-2-thiénylcarbonyl)-1-pipérazinyl]-4-éthoxypyrimidine,
- chlorhydrate de 2-[4-(3-chloro-2-thiénylcarbonyl)-1-pipérazinyl]-4-éthoxypyrimidine,
- 4-éthoxy-2-{4-[2-(trifluorométhyl)benzoyl]-1-pipérazinyl}pyrimidine,
- chlorhydrate de 4-éthoxy-2-{4-[2-(trifluorométhyl)benzoyl]-1-pipérazinyl}pyrimidine,
- 2-[4-(2-méthylbenzoyl)-1-pipérazinyl]-4-méthoxypyrimidine,
- chlorhydrate de 2-[4-(2-méthylbenzoyl)-1-pipérazinyl]-4-méthoxypyrimidine,
- 2-[4-(4-fluorobenzoyl)-1-pipérazinyl]-4-isopropoxypyrimidine,
- chlorhydrate de 2-[4-(4-fluorobenzoyl)-1-pipérazinyl]-4-isopropoxypyrimidine,
- 4-isopropoxy-2-{4-[2-(trifluorométhyl)benzoyl]-1-pipérazinyl}pyrimidine,
- chlorhydrate de 4-isopropoxy-2-{4-[2-(trifluorométhyl)benzoyl]-1-pipérazinyl}pyrimidine,
- 2-[4-(3-chloro-2-thiénylcarbonyl)-1-pipérazinyl]-4-isopropoxypyrimidine,
- chlorhydrate de 2-[4-(3-chloro-2-thiénylcarbonyl)-1-pipérazinyl]-4-isopropoxypyrimidine,
- 2-[4-(cyclohexylcarbonyl)-1-pipérazinyl]-4-méthoxypyrimidine,
- chlorhydrate de 2-[4-(cyclohexylcarbonyl)-1-pipérazinyl]-4-méthoxypyrimidine,
- 4-éthoxy-2-[4-(4-fluorobenzoyl)-1-pipérazinyl]pyrimidine,
- chlorhydrate de 4-éthoxy-2-[4-(4-fluorobenzoyl)-1-pipérazinyl]pyrimidine,
- 2-[4-(2-thiazolilcarbonyl)-1-pipérazinyl]-4-méthoxypyrimidine,
- 2-[4-(2-aminobenzoyl)-1-pipérazinyl]-4-méthoxypyrimidine,
- chlorhydrate de 2-[4-(2-aminobenzoyl)-1-pipérazinyl]-4-méthoxypyrimidine,
- 2-[4-(3-fluoro-2-thiénylcarbonyl)-1-pipérazinyl]-4-méthoxypyrimidine,
- chlorhydrate de 2-[4-(3-fluoro-2-thiénylcarbonyl)-1-pipérazinyl]-4-méthoxypyrimidine,
- acide 2-[4-(4-méthoxy-2-pyrimidinil)-1-pipérazinylcarbonyl]benzoïque,
- 2-[4-(2-acétoxybenzoyl)-1-pipérazinyl]-4-méthoxypyrimidine,
- 2-[4-(2-hydroxybenzoyl)-1-pipérazinyl]-4-méthoxypyrimidine,
- benzoate de sodium 2-[4-(4-méthoxy-2-pyrimidinyl)-1-pipérazinylcarbonyle],
- hydrochlorate de 2-[4-(2-hydroxybenzoyl)-1-pipérazinyl]-4-méthoxypyrimidine,

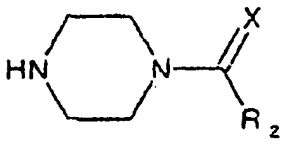
- 4-méthoxy-2-[4-(2-méthoxybnzoyl)-1-pipérazinyl]méthoxypyrimidine, et
- 4-éthoxy-2-[4-(2-pyridylcarbonyl)-1-pipérazinyl]pyrimidine.

11. Procédé pour la préparation d'un composé de formule générale (I), dans laquelle X représente un atome d'oxygène, selon la revendication 1, qui comprend la réaction d'un dérivé de chloropyrimidine de formule (III)



(III)

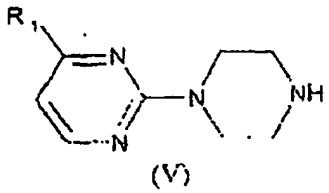
dans laquelle R_1 a la signification définie dans la revendication1,
avec un dérivé de pipérazine de formule générale (IV)



(IV)

dans laquelle R_2, a la signification définie dans la revendication 1 et X représente un atome d'oxygène.

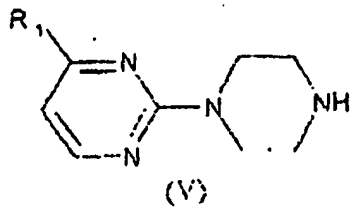
12. Procédé pour la préparation d'un composé de formule générale (I) dans laquelle X représente un atome d'oxygène, selon la revendication 1, qui comprend la réaction d'une amine de formule (V)



(V)

dans laquelle R_1 a la signification définie dans la revendication 1,
avec un acide carboxylique de formule R_2COOH (VI) ou avec un sel dudit acide, où R_2 a la signification définie dans la revendication 1.

13. Procédé pour la préparation d'un composé de formule (I) dans laquelle X représente un atome d'oxygène, selon la revendication 1, qui comprend la réaction d'une amine de formule (V)



(V)

dans laquelle R_1 a la signification définie dans la revendication 1
avec un réactif dérivé R_2COY (VII), où R_2 a la signification définie dans la revendication 1 et Y représente un atome d'halogène, un groupe azide, un groupe 1-imidazolyle, un groupe O-CO-R^4, où R_4 représente un radical alkyle de 1 à 6 atome de carbone ou un radical aryle, optionnellement substitué par un ou plusieurs atomes d'halogène, ou un groupe OR_3 où R_3 représente un groupe aromatique ou un ou deux anneaux substitués par un ou plusieurs atomes d'halogène ou des radicaux nitro, ou N-succinimide.

14. Procédé pour la préparation d'un composé de formule générale (I) dans laquelle X représente un atome de soufre, selon la revendication 1, qui comprend la réaction d'un composé de formule générale (I) dans laquelle X représente un atome d'oxygène, avec un réactif de Lawesson, (2,4-bis(4-méthoxyphényl)-1,3,2,4-dithiadiphosphaéthano-2,4-bi-dioxyde de soufre), ou avec du pentasulfure phosphoreux

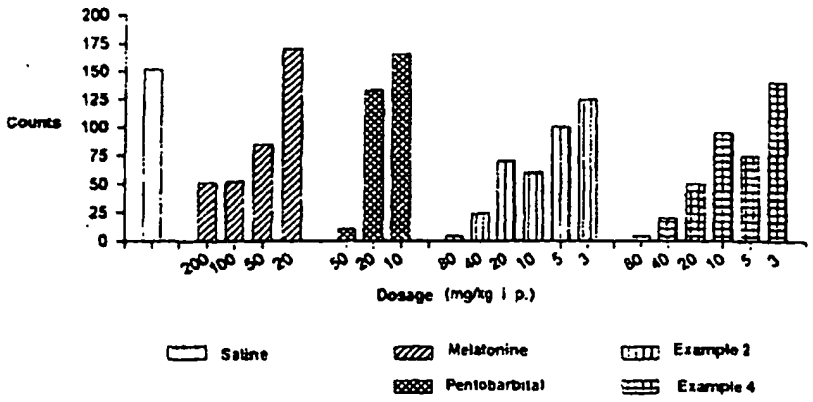
15. Procédé pour la préparation de sels physiologiquement acceptables des composés de formule générale (I), selon la revendication 1, laquelle comprend la réaction d'un composé de formule générale (I) avec un acide minéral ou un acide organique dans un solvant approprié.

16. Une composition pharmaceutique **caractérisée en ce qu'**elle contient, outre un excipient pharmaceutiquement acceptable, au moins un composé de formule générale (I) ou un de ses sels physiologiquement acceptables, selon les revendications 1 à 10.

17. Utilisation d'un composé de formule générale (I) ou leurs sels pharmaceutiquement acceptables, selon l'une quelconque des revendications 1 à 10, dans la fabrication d'un médicament avec de l'activité dans le système central nerveux des mammifères y compris l'homme.

18. Utilisation d'un composé de formule générale (I) ou leur sels pharmaceutiquement acceptable, selon l'une quelconque des revendications 1 à 10, dans la fabrication d'un médicament avec de l'activité sédative, anticonvulsive, analgésique, de relaxation musculaire, antitussive, anxiolytique, antipsychotique, antidépresseur, anti-ischémie cérébrale, anti-migraine, dans la fabrication d'un médicament pour traiter les troubles du sommeil, les maladies neurodégénératives, les troubles cognitifs et la maladies d'Alzheimer, les agentes inducteurs du sommeil ou anesthésiques généraux, pour les mammifères y compris l'homme.

Figure 1. Sedative activity: reduction in locomotive activity



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(54) DERIVATIVES OF ACYL-PIPERAZINIL-PYRIMIDINS, PREPARATION THEREOF AND APPLICATION AS MEDICAMENTS

DERIVATE VON ACYL-PIPERAZINIL-PYRIMIDINEN, IHRE HERSTELLUNG UND VERWENDUNG ALS MEDIKAMENT

DERIVES D'ACYLE-PIPERAZINIL-PYRIMIDINES, PREPARATION ET UTILISATION DE CES DERIVES COMME MEDICAMENTS

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